

DOCTORAL THESIS

The economics of malaria control: Opportunities, incentives, and risks on the road from control to elimination

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**The economics of malaria control:
Opportunities, incentives, and risks on the road from control to elimination**

Memòria de tesi doctoral presentada per **Joseph Russell Brew** per optar al grau de doctor/a per la Universitat de Barcelona, dirigida per **Elisa Sicuri** (Universitat de Barcelona i Imperial College), **Jacqueline Broerse** (Vrije Universiteit Amsterdam) and **Menno Pradhan** (Vrije Universiteit Amsterdam and Universiteit van Amsterdam).

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"Nature hath framed strange fellows in her time."

The Merchant of Venice
William Shakespeare

ACCOUNT OF STUDIES

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Article	Quartile	Impact factor
Researchers' perceptions of malaria eradication: findings from a mixed-methods analysis of a large online survey. Brew J , Pradhan M, Broerse J, Bassat Q. <i>Malaria Journal</i> . https://malariajournal.biomedcentral.com/articles/10.1186/s12936-020-03430-2	Q1	2.631
Foreign direct investment, corporate social responsibility, and malaria control in Mozambique - trends, risks, and opportunities. Brew J , Aerts C, Sicuri E. <i>Development Policy Review</i> (under review). https://github.com/joebrew/fdi_moz		
Evidence of high bednet usage from a list randomization in rural Gambia. Brew J , Pinder M, Dalessandro U, Lindsay SW, Jones C, Sicuri E. <i>Malaria Journal</i> . https://dx.doi.org/10.21203/rs.2.17453/v1	Q1	2.631
Evidence of high bednet usage from a list randomization in rural Gambia. Brew J , Pinder M, Dalessandro U, Lindsay SW, Jones C, Sicuri E. <i>Malaria Journal</i> . https://dx.doi.org/10.21203/rs.2.17453/v1	Q1	2.631
A systematic review of the incremental costs of implementing a new vaccine in the expanded program of immunization in Sub-Saharan Africa. Brew J , Sauboin C. <i>Medical Decision Making Policy & Practice</i> . https://doi.org/10.1177%2F2381468319894546		2.309
Mapping the potential use of endectocide-treated cattle to reduce malaria transmission. Imbahale S, Montaña J, Brew J , Paaijmans K, Rist C, Chaccour C. <i>Nature Scientific Reports</i> . https://www.nature.com/articles/s41598-019-42356-x	Q1	4.576
Is malaria control profitable? Return on investment of residential fumigation at a sugarcane processing facility. Brew J , Sicuri E, Pradhan M, Gondo K. Intention to submit to <i>Journal of Health Economics</i> . https://docs.google.com/document/d/1bUWRBCgVcgjSPHchIQxiTG8Vwv5hV1GLU4Tlu386sWA/edit#		

RESUMEN

Planteamiento del problema

El problema del control de la malaria es uno de (a) piezas funcionales y (b) un conjunto roto. Es decir, si existen los componentes necesarios para eliminar la enfermedad por completo (intervenciones eficaces e incentivos suficientes para llevarlas a cabo), ¿por qué se ha estancado el progreso hacia la eliminación?

La razón por la que los individuos y las organizaciones deciden comprometerse e invertir, o no, en actividades de control de la malaria, es una cuestión de incentivos. Pero los incentivos para el control de la malaria no existen en el vacío: compiten con otras prioridades sanitarias, están condicionados por la participación de otros en actividades de control de la malaria y se ajustan en función de la percepción de la probabilidad de "éxito" de esas actividades. Además, la correcta enumeración de los incentivos depende en gran medida de la disponibilidad y la calidad de los datos en los que se basan. Comprender los incentivos para el control de la malaria es complejo pero necesario para entender por qué se ha estancado el progreso hacia su erradicación.

Objetivo

El objetivo general de esta investigación es conocer los incentivos a favor y en contra del control y la eliminación de la malaria, tanto a nivel de individuos como de organizaciones. Esta investigación persigue este objetivo mediante (a) la exploración de asociaciones no explotadas con partes interesadas atípicas en el control de la malaria a través de una cuantificación de los costes y beneficios de participar en actividades de control de la malaria; (b) la evaluación de la incertidumbre en relación con el coste de las intervenciones relacionadas con el control y la eliminación; (c) el cálculo de la probabilidad y la escala temporal para la erradicación, así como los factores facilitadores y las barreras; y (d) la evaluación de la fiabilidad de algunos de los datos que utilizamos para medir las actividades relacionadas con el control.

Preguntas de investigación e hipótesis

Las preguntas de investigación que se examinan en esta disertación son:

1. ¿Dónde existen oportunidades para ampliar el conjunto de partes interesadas y financiadores que participan en el control de la malaria?
2. ¿Cuál es la probabilidad y el plazo para la erradicación de la malaria?
3. ¿Cuánto cuesta el control de la malaria?
4. ¿Cuáles son los efectos de las actividades de control y eliminación de la malaria?
5. ¿En qué medida podemos confiar en los datos generados por la investigación relacionada con la malaria?

Las hipótesis de esta investigación son, respectivamente

1. No existen oportunidades significativas para ampliar el conjunto de partes interesadas y financiadores que participan en el control de la malaria, porque los incentivos económicos para ampliar los esfuerzos de control no son suficientes.
2. La probabilidad y el plazo de la erradicación global de la malaria, tal como los perciben los investigadores de la malaria, es menor y más larga de lo que sugiere el discurso institucional; esta brecha puede explicarse por la necesidad de las

instituciones de proyectar optimismo para atraer financiación, y la vacilación de los investigadores a la hora de expresar pesimismo por razones de sesgo de deseabilidad social.

3. El control de la malaria es prohibitivo en muchos contextos, lo que hace que la ampliación del control (esfuerzos de eliminación) sea económicamente inviable.
4. Los efectos de las actividades e intervenciones de control de la malaria son positivos, pero no lo suficientemente grandes como para compensar los costes financieros.
5. Los efectos de las actividades de control de la malaria pueden ser menores de lo que los investigadores perciben a través de los datos sesgados que recopilan; esta brecha entre la realidad y el registro podría explicar en parte el fracaso histórico de las campañas de erradicación y el actual estancamiento del progreso.

Marco teórico

Los fundamentos teóricos de esta investigación se basan en tres modelos fundacionales: (1) la teoría del capital humano, (2) la teoría de la elección racional y (3) el modelo socioecológico. En consonancia con los dos primeros, se asume que los individuos y las empresas son actores racionales que maximizan la utilidad. Pero, en consonancia con el tercero, también reconoce que las decisiones se toman en un entorno complejo e interactivo con múltiples niveles dinámicos.

Enfoque de la investigación

Esta investigación se realizó en el marco del "diseño emergente". Es decir, no todas las preguntas de la investigación se concibieron a priori, sino que fueron surgiendo a medida que se generaban los resultados. A alto nivel, la investigación sigue tres núcleos temáticos. En primer lugar, examino el papel del sector privado en el control de la malaria. En segundo lugar, trato de entender si los sistemas de información que utilizan los investigadores para controlar las intervenciones contra la malaria son en sí mismos defectuosos. Es decir, examino hasta qué punto podríamos estar midiendo mal los insumos de las iniciativas de control de la malaria, lo que podría explicar por qué los resultados de estas iniciativas no han sido óptimos. Por último, busco nuevas fuentes de datos que exploren cómo y cuándo podría lograrse la erradicación de la malaria, identificando las oportunidades en las que las intervenciones no tradicionales podrían ser más eficaces, y cuantificando los costes de despliegue de una hipotética intervención futura.

Este enfoque abarca los 6 estudios siguientes:

Estudio 1 (Percepciones de los investigadores sobre la erradicación de la malaria: resultados de un análisis de métodos mixtos de una gran encuesta en línea)

- Los investigadores son pesimistas silenciosos, y dan poca credibilidad a la probabilidad de erradicación a pesar de que el discurso institucional apunta a su viabilidad y a un plazo relativamente corto.
- Muchos participantes en el estudio atribuyeron la incapacidad de erradicar la malaria a corto plazo a la inadecuación de las herramientas técnicas actuales (es decir, a la necesidad de innovación), a la presencia de retos sistémicos (como la pobreza y la falta de voluntad política) y a la complejidad general de la dinámica de transmisión de la malaria.

Estudio 2 (Inversión extranjera directa, responsabilidad social corporativa y control de la malaria en Mozambique: tendencias, riesgos y oportunidades)

- La responsabilidad social de las empresas y la inversión extranjera directa tienen muchas posibilidades de desempeñar un papel importante en el control de la malaria, si se coordinan con el sector público y se aseguran contra la volatilidad del mercado; sin embargo, una dependencia demasiado grande de las iniciativas privadas para el bien público de la eliminación de la malaria es una estrategia arriesgada.
- Dado el papel desproporcionado de las empresas extranjeras en las mayores industrias de Mozambique (gas y minería en el norte, caña de azúcar en el sur), existe la oportunidad de que el gobierno ejerza una presión positiva para participar en el control de la malaria, así como de coordinar las actividades para evitar la redundancia público-privada y reducir el riesgo de dependencia excesiva.

Estudio 3 (Evidencia de un alto uso de mosquiteros a partir de una lista aleatoria en la zona rural de Gambia)

- Entre los habitantes de las zonas rurales de Gambia que siguieron a una gran campaña de distribución, el uso de mosquiteros mediante técnicas de obtención de datos anónimos parece muy elevado, lo que sugiere que la preocupación por el mal uso y el desuso de los mosquiteros puede ser exagerada en algunos contextos.
- Aunque el método de aleatorización de listas puede ayudar a reducir ciertos tipos de sesgos (como el sesgo de deseabilidad social), es novedoso y no está validado, y puede provocar a su vez otros tipos de sesgos.
- Para el caso concreto de la investigación sobre el uso de los LLIN, es necesario investigar más sobre la validez interna del método.

Estudio 4 (Una revisión sistemática de los costes incrementales de la implementación de una nueva vacuna en el programa ampliado de inmunización en el África subsahariana)

- Es posible generar estimaciones de los costes operativos de la implementación de una vacuna contra la malaria en el África subsahariana, pero se espera que los costes varíen mucho en función de la ubicación y del grado de verticalización o integración en los programas sanitarios existentes.
- Hay una necesidad urgente de estandarizar los estudios de costes para mejorar la comparabilidad y hacer estimaciones más precisas.

Estudio 5 (Trazado del uso potencial del ganado tratado con endectocida para reducir la transmisión de la malaria)

- El tratamiento con endectocida del ganado para la reducción de la transmisión de la malaria debería ser prioritario en África Occidental, donde el solapamiento entre (a) la prevalencia de la malaria entre los niños, (b) la densidad de los vectores zoófilos de la malaria y (c) la presencia de ganado es mayor.
- Las intervenciones combinadas dirigidas a los mosquitos zoofílicos también pueden ser valiosas en las regiones del mundo donde el paludismo es endémico y en las que es frecuente la presencia de otros animales (como los cerdos en el sur de África y el ganado vacuno y caprino en el subcontinente indio).
- La eficacia de las intervenciones combinadas dependerá en gran medida del grado de zoofilia del vector y de las prácticas ganaderas de la zona (proximidad a los

dormitorios humanos, etc.); por lo tanto, dichas intervenciones deben evaluarse con un enfoque ultralocalizado.

Estudio 6 (¿Es rentable el control de la malaria? Retorno de la inversión de la fumigación residencial en una instalación de procesamiento de caña de azúcar)

- La inversión de una empresa en medidas de prevención de la malaria (fumigación residual de interiores) no sólo protegió la salud de sus trabajadores, sino que también supuso una reducción de las ausencias por un valor superior a los costes de administración del programa.
- Este hallazgo sugiere que no es descabellado prever que el sector privado podría desempeñar un papel importante en los esfuerzos de control y eliminación de la malaria, si se lleva a cabo en coordinación con las políticas e intervenciones gubernamentales.
- También implica que las empresas privadas son beneficiarias directas de las actividades de control de la malaria; en consecuencia, independientemente de quién lleve a cabo las actividades reales, implicar al sector privado en su coordinación y financiación puede ser beneficioso para todos.

Discusión y conclusión

Los incentivos para el control de la malaria existen para las organizaciones, y las empresas que participan en el control de la malaria pueden generar un beneficio (estudio 6), además de beneficios no tangibles en términos de relaciones públicas (estudio 2). Los individuos también consideran que los incentivos para el control de la malaria son suficientes para justificar un alto nivel de compromiso (estudio 3). A pesar de la existencia de estos incentivos, un retroceso en el progreso de los últimos años en la eliminación de la malaria sugiere que los incentivos no se perciben como suficientes para justificar la ampliación, en parte debido al escepticismo respecto a la probabilidad de eliminación y a la complejidad (estudio 1), así como a un desconocimiento general de las métricas utilizadas para cuantificar el control de la malaria y las evaluaciones de eficacia (estudios 3, 4, 6).

El control de la malaria podría acelerarse mediante la innovación técnica (estudio 1), pero también pueden ser útiles otras formas de innovación, como la ampliación del conjunto de partes interesadas que participan en el control coordinado de la malaria (estudio 2), así como la incorporación de métodos que tienen beneficios para el control de la malaria a pesar de no ser su objetivo principal (estudio 5). La falta de inversión en la malaria puede estar motivada en parte por la falta de datos estandarizados, transparentes y comparables sobre los costes (estudio 4) y los beneficios económicos (estudio 1) del control de la malaria.

Los resultados generales de esta disertación apuntan a que los datos sobre los insumos para el control de la malaria están envueltos en la complejidad, lo que hace que incluso quienes trabajan directamente en las actividades de control desconozcan hasta qué punto sus datos son fiables y la eficacia de las actividades en las que participan. El efecto de la complejidad es un desconocimiento práctico de los incentivos del control de la malaria, que es un probable culpable de la falta de inversión. La complejidad puede contrarrestarse con más claridad, estandarización y transparencia tanto en los insumos para el control de la malaria (coste de las actividades) como en los resultados (cuantificación de los efectos).

Las limitaciones de estos estudios deberían investigarse más a fondo: la falta de estandarización en la categorización de los costes en los programas de control de la malaria, el sesgo de selección en las encuestas de obtención de percepciones, la necesidad de validar métodos novedosos para evaluar los comportamientos individuales a través de autoinformes sesgados, y la comprobación de la generalización de la conclusión de que una empresa privada que invierte en la reducción de la malaria entre los trabajadores puede ser rentable.

SUMMARY

Problem statement

The problem of malaria control is one of (a) functional pieces and (b) a broken whole. That is, if the necessary components for eliminating the disease entirely (effective interventions and sufficient incentives to pursue them) exist, why has progress towards elimination stalled?

Why individuals and organizations choose to engage and invest, or not, in malaria control activities, is a question of incentives. But incentives for malaria control do not exist in a vacuum: they compete with other health priorities, they are conditioned by others' engagement in malaria control activities, and they are adjusted as a function of the perception of the likelihood of those activities' "success". Furthermore, the correct enumeration of incentives is highly dependent on the availability and quality of the data on which they're built. Understanding incentives for malaria control is complex but necessary in order to understand why progress towards malaria eradication has stalled.

Aim

The general aim of this research is to gain insight into incentives for and against malaria control and elimination at the level of both individuals and organizations. This research pursues this aim by (a) exploring unexploited partnerships with atypical stakeholders in malaria control through a quantification of costs and benefits of engaging in malaria control activities; (b) assessing uncertainty in regards to the cost of control and elimination-related interventions; (c) calculating the likelihood and time-scale to eradication, as well as facilitating factors and barriers; and (d) assessing the reliability of some of the data we use to gauge control-related activities.

Research questions and hypotheses

The research questions examined in this dissertation are:

1. Where do opportunities exist for enlarging the body of stakeholders and funders involved in malaria control?
2. What is the likelihood of and time-frame to malaria eradication?
3. How much does malaria control cost?
4. What are the effects of malaria control and elimination activities?
5. To what extent can we rely on the data generated by malaria-related research?

The hypotheses in this dissertation are, respectively:

1. Significant opportunities for enlarging the body of stakeholders and funders involved in malaria control do not exist, because the economic incentives for scaled-up control efforts are not sufficient.
2. The likelihood of and time-frame to global malaria eradication, as perceived by malaria researchers, is lower and longer than institutional discourse would suggest; this gap can be explained by the need for institutions to project optimism in order to attract funding, and the hesitance of researchers to express pessimism for reasons of social desirability bias.
3. Malaria control is prohibitively expensive in many contexts, making scaled-up control (elimination efforts) economically unfeasible.

4. The effects of malaria control activities and interventions are positive, but not sufficiently sized to offset the financial costs.
5. The effects of malaria control activities may be less than what researchers perceive via the biased data which they collect; this gap between reality and registration could partially explain the historical failure of eradication campaigns and the current stall in progress.

Theoretical framework

The theoretical underpinnings of this research rely on three foundational models: (1) human capital theory, (2) rational choice theory, and (3) the social-ecological model. In line with the first two, it assumes that individuals and firms are rational, utility-maximizing actors. But, in line with the latter, it also recognizes decisions are made in a complex, interactive environment with multiple, dynamic levels.

Research approach

This research was carried in the framework of “emergent design”. That is, not all research questions were conceived *a priori*, but rather emerged as results were generated. At a high-level, the research follows three cores themes. First, I examine the role of the private sector in malaria control. Second, I seek to understand if the information systems researchers use for monitoring malaria interventions are themselves flawed. That is, I examine the extent to which we might be mismeasuring the *inputs* of malaria control initiatives, which could explain why the *outputs* of these initiatives have been suboptimal. Finally, I seek novel data sources that explore how and when malaria eradication might be achieved, identifying opportunities where non-traditional interventions might be most effective, and quantifying the roll-out costs of a hypothetical future intervention.

This approach encompasses the 6 below studies:

Study 1 (Researchers’ perceptions of malaria eradication: findings from a mixed-methods analysis of a large online survey)

- Researchers are silent pessimists, placing low probability on the likelihood of eradication despite institutional discourse pointing to its feasibility and relatively short timeline.
- Many study participants attributed the inability to eradicate malaria in the short-term to the inadequacy of current technical tools (i.e., a need for innovation), the presence of systemic challenges (such as poverty and lack of political will), and the general complexity of malaria transmission dynamics.

Study 2 (Foreign direct investment, corporate social responsibility, and malaria control in Mozambique - trends, risks, and opportunities)

- There exists ample opportunity for corporate social responsibility and foreign direct investment to play an important role in malaria control, if coordinated with the public sector and insured against market volatility; however, too heavy a reliance on private initiatives for the public good of malaria elimination is a risky strategy.
- Given the disproportionate role of foreign firms in Mozambique’s largest industries (gas and mining in the north, sugarcane in the south), there exists an opportunity for government to exert positive pressure to engage in malaria control, as well as to

coordinate activities so as to avoid public-private redundancy and reduce the risk of overreliance.

Study 3 (Evidence of high bednet usage from a list randomization in rural Gambia)

- Among rural Gambians following a large distribution campaign, bednet usage using anonymizing data elicitation techniques appears very high, suggesting that concerns about misuse and disuse of bednets may be overstated in some contexts.
- Though the list randomization method may help reduce certain kinds of biases (such as social desirability bias), it is novel and unvalidated, and may in turn provoke other kinds of biases.
- For the specific case of research on LLIN usage, further research is needed regarding the method's internal validity.

Study 4 (A systematic review of the incremental costs of implementing a new vaccine in the expanded program of immunization in Sub-Saharan Africa)

- It is feasible to generate estimates for the operational costs of implementing a malaria vaccine in Sub-Saharan Africa, but costs are expected to vary widely as a function of location, and degree of verticalization or integration into existing health programs.
- There is an urgent need for standardization in costing studies so as to improve comparability and render more accurate estimates.

Study 5 (Mapping the potential use of endectocide-treated cattle to reduce malaria transmission)

- Endectocide treatment of cattle for malaria transmission reduction should be prioritized in West Africa, where the overlap between (a) the prevalence of malaria among children, (b) the density of zoophilic malaria vectors and (c) the presence of cattle is greatest.
- Combinatory interventions targeting zoophilic mosquitoes may also be of value in regions of the malaria-endemic world where other livestock are common, (such as swine in southern Africa and cattle/goats in the Indian subcontinent).
- The effectiveness of combinatory interventions will hinge largely on the degree of zoophilia of the vector, and the area's animal husbandry practices (proximity to human sleeping quarters, etc.); accordingly, such interventions should be evaluated with an ultra-localized approach.

Study 6 (Is malaria control profitable? Return on investment of residential fumigation at a sugarcane processing facility)

- A firm's investment in malaria prevention measures (indoor residual spraying) not only protected the health of their workers, but also led to a reduction in absences worth more than the costs of administering the program.
- This finding suggests that it is not unreasonable to anticipate that the private sector could play an important role in malaria control and elimination efforts, if carried out in coordination with government policies and interventions.
- It also implies that private firms are direct beneficiaries of malaria control activities; accordingly, regardless of who carries out the actual activities, involving the private sector in their coordination and financing may be beneficial to all.

Discussion and conclusion

Incentives for malaria control exist for organizations, and firms engaging in malaria control can generate a profit (study 6), in addition to non-tangible benefits in terms of public relations (study 2). Incentives for malaria control are also perceived by individuals to be sufficient enough to justify high levels of engagement (study 3). Despite the existence of these incentives, a regression in progress in recent years in malaria elimination suggests that the incentives are not perceived as sufficient to justify scale-up, in part due to scepticism regarding the likelihood of elimination and complexity (study 1), as well as an overall unfamiliarity with the metrics used for quantifying malaria control and effectiveness evaluations (studies 3, 4, 6).

Malaria control could be accelerated by technical innovation (study 1), but other forms of innovation may be useful, such as expanding the body of stakeholders involved in coordinated malaria control (study 2) as well as enlisting methods which have benefits for malaria control despite it not being its principal aim (study 5). Under-investment in malaria may be partly motivated by a lack of standardized, transparent, comparable data on the costs (study 4) and economic benefits (study 1) of malaria control.

The overall results of this dissertation point toward data on malaria control inputs being shrouded in complexity, causing even those who are working directly in control activities to be unaware of the extent to which their data is reliable and the effectiveness of the activities in which they engage. The effect of complexity is a practical ignorance of malaria control incentives, which is a likely culprit in under-investment. Complexity can be countered with more clarity, standardization, and transparency on both malaria control inputs (cost of activities) and outputs (quantification of effects).

Further research should be directed at the limitations of these studies: a lack of standardization in cost categorization in malaria control programs, selection bias in perception elicitation surveys, the need for validation of novel methods for assessing individual behaviors via debiased self-report, and testing the generalizability of the finding that a private firm investing in reducing malaria among workers can be profitable.

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1. Introduction

1.1 General Introduction and problem statement

The ever-present problem of malaria

Malaria is among the oldest diseases known to humankind. References to seasonal fever outbreaks appear on clay tablets from Mesopotamia (Institute of Medicine, Board on Global Health, and Committee on the Economics of Antimalarial Drugs 2004). Ancient Egyptian, Indian, Chinese, and Greek literature all contain references to malaria (“Malaria: A Brief History” 2016), and the name itself (meaning “bad air”) (Hempelmann and Krafts 2013) evokes a bygone era when much was known about the firsthand experience of the disease, but little was known about its transmission. In his essay “On Airs, Waters, and Places”, Hippocrates spoke of “marsh fevers” among those who lived near water (Hippocrates 2007). This general understanding that the quality of air was malaria’s causal agent persisted until the 1800s.

Prior to humanity’s understanding of the origins of malaria, progress in malaria control was likely accidental. That is, urbanization and industrial water management led to reductions in malaria’s burden even though these reductions did not figure into the intentions of those carrying out the interventions. That said, the changing epidemiology of malaria, caused by the changes to landscapes which came from industrialization, may have figured into Charles E. Johnson’s challenge of the millenia-old “miasma” (bad air) theory. “These are some of the facts and circumstances which have induced me to abandon the miamatic hypothesis”, he wrote to his colleagues in 1851. “No chemical analysis, so far, has been able to detect [miasma]; no microscopic investigation... there is no truth in the doctrine miasmatic origin of disease” (Johnson and Medical Society of the State of North Carolina 1851).

Scientists’ understanding of malaria was accelerated by the economic incentives that came with colonialism. To some extent, the emergence of the field of “global health” itself came as a result of the magnitude of the problem of fever among colonists. After all, as Albert Freeman Africanus King wrote in 1883, “of all human races the white is most susceptible to marsh-fevers, the black least so” (Daniels 1950). Imperial Europeans and Americans needed to better understand the origin of tropical fevers in order to mitigate their economic effects, and with these incentives aligned, progress came quick. By the late 20th century, colonialism-fueled science had made clear that malaria was mosquito-driven. By the end of the century, the aetiological mystery was solved: parasites were observed in a malaria-stricken patient’s blood (Anderson and Laveran 1893).

With this knowledge in hand, and with most of Africa colonized by Europeans, the early 20th century saw rapid progress in malaria control. Much of it continued to be the secondary effects of economic development (specifically from swamp drainage and housing improvement), but pesticides targeting the malaria vector – the mosquito – also played a significant role. As of 1900, it is estimated that 53% of the world’s surface was at risk of malaria; a century later, that number was sliced in half to 27%. In terms of population, this meant a reduction from 77% to approximately 50% (Hay et al. 2004). In other words, the

path to global eradication had begun, even though eradication was not a familiar concept to the scientific community at the time.

Success in suppressing seasonal malaria outbreaks coincided geographically and temporally with colonial development projects. In the Panama Canal zone, greater than 1% of workers died annually due to malaria in 1906; 3 years later, thanks largely to environmental health interventions, that number was reduced to approximately 1 in 1,000 (“The Path between the Seas: The Creation of the Panama Canal, 1870-1914,” n.d.). Though the malaria control interventions – swamp drainage, bush cutting, larvicide, quinine distribution, and door and window screening – were primarily aimed at protecting workers, there was a positive spillover to nearby local populations: deaths from malaria for the population at large dropped from 16 per 1,000 in 1906 to 2.6 per 1,000 in 1909 (CDC-Centers for Disease Control and Prevention 2009). Though the overall effect of the canal on health is difficult to quantify, in the specific realm of malaria, it is clear that public health benefited from private malaria control.

Similar privately-driven malaria control interventions were taking place simultaneously in other parts of the world. In Asia, malaria control was driven largely by plantation owners (Watson 1908), whereas in Africa it was largely mining operations (Utzinger et al. 2002). Latin America also saw a mix of malaria control efforts at large mines and plantations (Killeen et al. 2002). These campaigns were decentralized, had no ambitions of elimination, and only had limited public health intentions, and were primarily profit-driven. Progress in malaria control continued through the first half of the 20th century, but not at the explosive rate of the century's first decade (Ward and Harrison 1979).

Whereas the early century jump in malaria control progress was largely due to infrastructural improvements, and driven by colonial ambitions, malaria control went through another acceleration phase in the mid-20th century, thanks to both chemical and geopolitical factors. The chemical factor was the wide scale emergence of DDT (dichlorodiphenyltrichloroethane) as an insecticide, and the geopolitical factor was (a) the deployment of European and American troops to the Pacific during the second world war followed by (b) the emergence of supranational organizations (United Nations and the World Health Organisation) thereafter.

The eradication era

“Now we know exactly... the schedule of an eradication campaign which will last four or five years followed by three years of consolidation”

-UNICEF Americas Regional Director, September Meeting, New York, 1955

The “eradication era” refers to the 2-decade period following the second world war (Hay et al. 2004). During this time, large “first-world” countries eliminated malaria (or came effectively close to elimination) thanks to (a) the resources available in the post-war economic boom, (b) the use of DDT, and (c) large-scale infrastructure projects in water management. The United States, along with southern Europe and parts of Northern Africa, also reduced annual autochthonous malaria cases to zero. In light of this progress, the World Health Organisation (WHO) set out on what at the time seemed a realistic campaign to completely eradicate malaria: in 1955, at its 8th World Health Assembly, the Global Malaria Eradication Programme (GMEP) was announced. The change in strategy was

radical, but meant to be radically transformative. Instead of the decentralized approach which characterized the early 20th century's progress, the GMEP would oversee a global, expert-driven campaign to eliminate malaria even from those areas where the stand-alone costs of doing so might otherwise not be deemed reasonable.

The eradication era ended almost as abruptly as it began. Though the centralized approach and ambitious vision helped foster support and donations, when expectations diverged from reality (as was the case in the massive resurgence of malaria cases in near-elimination contexts like Sri Lanka), disillusionment set in ("Malaria Consortium" n.d.). Furthermore, the top-down approach was successful in mobilizing resources, but was not able to integrate into local healthcare systems or respond differentially to the distinct social, political, and economic realities of malarious regions. In some ways, the cause of the GMEP's ambitious optimism – the effectiveness of DDT – was also in part the reason for its decline. By the time Rachel Carson published "Silent Spring" in 1962 (Drury 1963), documenting the adverse environmental effects caused by the widespread use of DDT, it had already become clear that the GMEP would not succeed in its mission. The "eradication era" ended, and malaria resurgence followed. By 1969, in light of stalling progress, parasite resistance to chloroquine, mosquito resistance to DDT, and shrinking donations, the WHO formally abandoned the campaign (Mendis et al. 2009).

Success with country-specific elimination: another chance at eradication?

From the 1970s through the 1990s, progress towards malaria eradication was stalled. Efforts were primarily at the national-level and aimed firmly at control rather than elimination. Political instability in recently independent African states lead to an outsized role of the private sector for malaria control. As with the early century's mining and plantation initiatives, these activities had positive public health externalities, but public health was not their primary intention. Malaria increased in some areas and decreased in others, but on the whole progress had stalled, or even reversed. Given the decreasing effectiveness of the arsenal of tools due to increasing resistance, deaths from malaria increased through the 1990s (Trape et al. 1998).

In reaction to these changes, and thanks to new therapies and interventions, at the turn of this century, the world community began looking again at national elimination, and worldwide eradication, as realistic goals. The Bill and Melinda Gates Foundation began active involvement in financing ambitious malaria projects in the early 2000s (Gross 2003). In response, a Lancet Editorial in 2007 asked the question "Is malaria eradication possible?"; the response was ambiguous, but characterized Gates' initiatives as "rightly challenging the global health community to ask itself whether it should not be more ambitious" ("Is Malaria Eradication Possible?" 2007).

That ambition emerged over the next decade. Researchers and funders began shifting their sights from control to elimination and eradication. The tone changed from eradication being a "challenge" to being a "goal" (Lancet and The Lancet 2011). The frequency with which the words "elimination" and "eradication" appeared in the research literature began to increase to levels not seen since the mid-century GMEP era (see figure 1.1). The conversation shifted from "if" to "how" and "when".

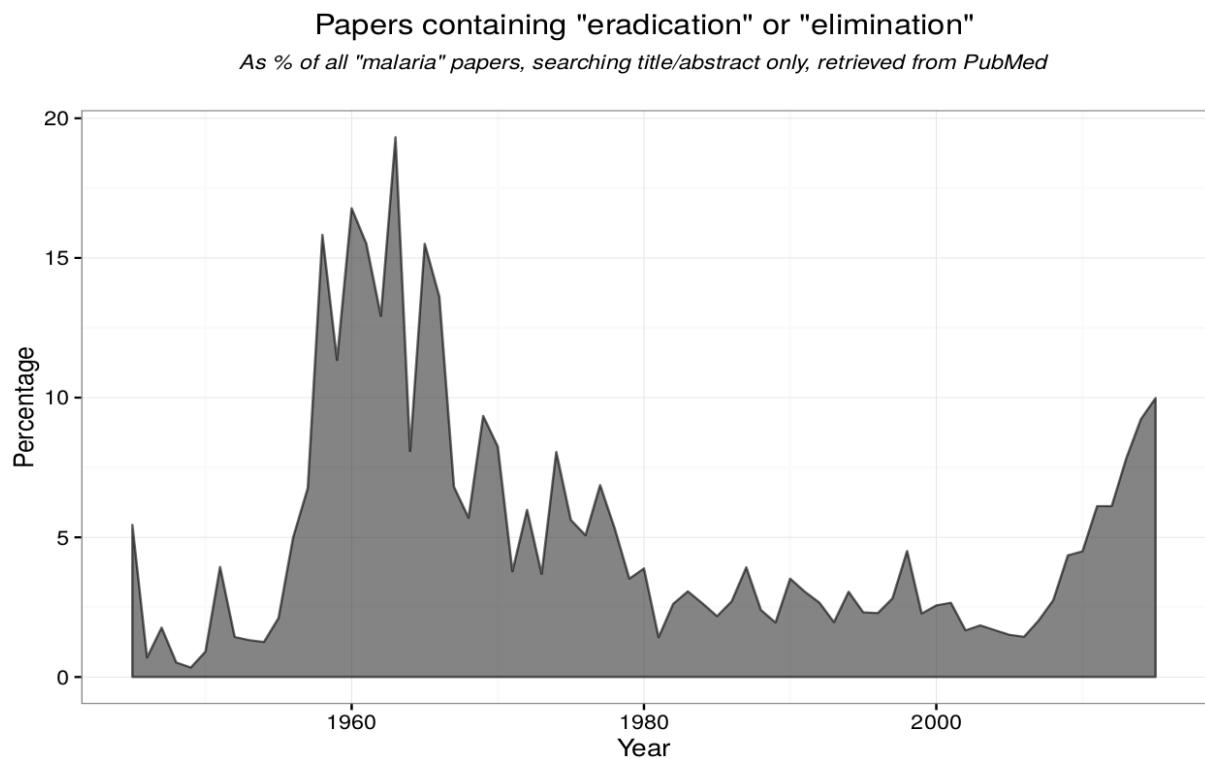


Figure 1.1: Percentage of papers on PubMed containing the terms “eradication” or “elimination” in the title or abstract, among all papers containing the word “malaria”. Data from PubMed; data aggregation and chart by Joe Brew.

Researchers were determined not to repeat the mistakes of the previous “era of eradication”. An evidence-based research agenda was established (Alonso et al. 2011), and energy began to consolidate. In 2014, Bill Gates declared that malaria could be eradicated “within a generation”. In 2015, the WHO set the goal of eliminating malaria in 35 new endemic countries in 15 years, and reducing all deaths by 90%. Everything, it seemed, was in place for rapid progress towards eradication.

Progress towards elimination and eradication efforts slowed, however, towards the end of the decade (see Figure 1.2). From 2015 to 2017, 55 countries saw an *increase* in the number of malaria cases. The WHO Strategic Advisory Group on Malaria Eradication (SAGME) acknowledged “stalling progress” and that meeting the 2015 targets was “unlikely” (World Health Organization 2019). And though the Lancet Commission argued that global eradication by 2050 was both a “necessary” and “attainable goal”, the timeline mentioned was 2050 (Feachem et al. 2019).

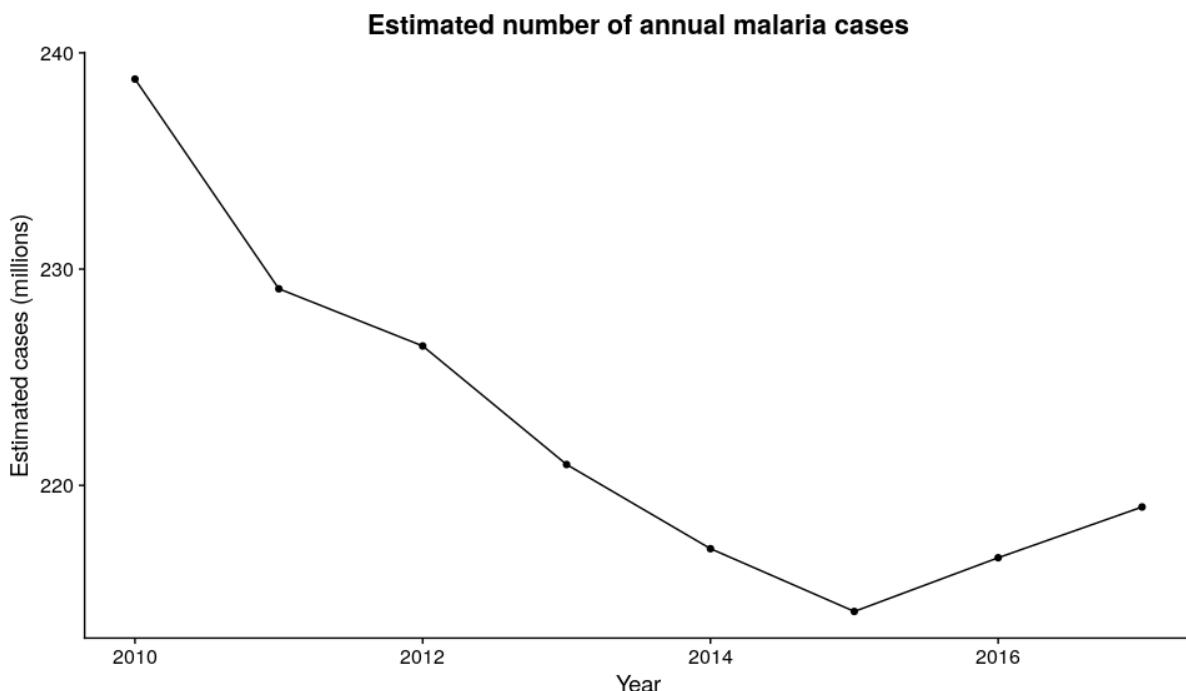


Figure 1.2: Estimated total number of annual malaria cases. Country-level data from the World Health Organization (<https://www.who.int/data/gho/data/indicators/indicator-details/GHO/estimated-number-of-malaria-cases>); data aggregation and chart by Joe Brew.

Problem statement

As was the case with the 1950s-60s eradication campaign of the WHO GMEP, stalling progress has forced the leaders of the world's second eradication campaign to soften their goals and timelines. In its most recent report, the WHO SAGME states that "we are certain that eradication by a specific date is not a promise we can make to the world just yet" (World Health Organization 2019). In other words, though the case for eradication is compelling, the research agenda is clear, and the technical requirements all seem to be in place, reality has – once again – diverged from expectations. History has, to some extent, repeated itself.

All the puzzle pieces for global malaria eradication appear to exist. Prevention methods are well-known, culturally acceptable, largely safe, and fairly affordable. Testing is rapid and cheap. Treatment is effective and almost universally available. Why then, again, does progress stall?

Malaria is what management scientist C. West Churchman might describe as a "wicked problem" (Surhone, Timpledon, and Marseken 2010). Like other "wicked problems", the characteristics of the problem and the resources available for solving it are in constant evolution, stakeholders in the issue have diverging views, and it is unique in both scope and nature. By the same token, the "solution" to the malaria "problem" depends on how the problem is framed – whether one says the problem as one of biomedical, geopolitical, or economic in nature.

Wicked problems are notoriously difficult to solve. Management research in the area suggests that progress is generally made when the problem is appropriately structured, and such a structuring requires the incorporation of new actors and viewpoints. In “Addressing Wicked Problems through Transdisciplinary Research” (Surhone, Timpson, and Marseken 2010; Pohl, Truffer, and Hirsch-Hadorn 2017), Pohl and his collaborators argue that the “recursive” and “inclusive” nature of transdisciplinary research can help in problem identification and structuring, since only an incorporation of all stakeholders’ views can lead to a comprehensive understanding of the true scope of a problem.

The problem of malaria is fundamentally one of (a) functional pieces and (b) a broken whole. The components for eliminating the disease entirely appear to exist, but the alignment of those components does not. In human behavior, collective alignment is a function of individual incentives. So, the reasonable conclusion one might make in trying to frame the problem of malaria is that the incentive must not exist, at the individual level, for eradication to take place (I specify the *individual* level, because it is clear from the evidence that the incentives at the *collective* level are more than abundant).

In this sense, national malaria elimination and global malaria eradication, and even local malaria control (to a lesser extent), can be conceptualized as a “public good” in that it is non-excludable (ie, it is not possible to exclude one from the positive externalities of another’s activities). Non-public actors (individuals and private firms) contribute to the production of this public good, but can be incentivized to contribute insufficiently to it, particularly when larger actors contribute disproportionately (Olson 2009). In this framing, an actor’s decision to “participate” or not in the provisioning of the public good of malaria control is a function of both that actor’s wealth, but also the relative distribution of wealth among other actors poised to potentially provision the same good (Bergstrom, Blume, and Varian 1986). Concretely, there may be a tendency for smaller actors (individuals and firms) to attempt to create the conditions in which larger actors (governments and international agencies) bear the burden of the provisioning of the good solely.

The fundamental irony of wicked problems is that defining them is itself part of the wickedness. That is, if the problem were easily defined, it would not be wicked. Thus, stating that individual incentives are not sufficient for the global eradication of malaria, or national elimination in many cases, is overly simplistic. The *wickedness* of the problem is in identifying where those incentives are missing, how they can be modified, and what mechanisms can be used to monitor the effect of their modification (and the unintended side-effects).

Tackling a wicked problem can be carried out using one of three strategies: (1) Collaborative, (2) Authoritative or (3) Competitive (Roberts 2000). Whereas the 1950s-60s GMEP campaign might be described as authoritative (insofar as it was centralized and sought to reduce the complexity of malaria by applying a one-size-fits-all approach), one might characterize the current eradication effort as collaborative, in that it strives to incorporate researchers and public health stakeholders in a more decentralized manner. But both the authoritative and collaborative approaches have, as discussed, lead to suboptimal progress towards the stated goals of eradication. Why is that?

My ingoing definition of the malaria problem is not that the tools available are inadequate, but rather that the incentives for their adoption are insufficient. This insufficiency of incentives assumption in some ways puts my research more in line with what Roberts' would call the “competitive” approach to wicked problem resolution. But I would argue that the malaria problem is more complex than her rubric permits. Harnessing competitive forces can be useful to progress in malaria (as was evidenced by the self-interested gains in malaria control from colonial efforts), but is not sufficient. The nature of malaria as a disease is in itself at the crossroads of competitive and collaborative dynamics, and is not without a dose of authoritative elements (i.e., medical professionals exercise a high, and necessary, degree of authority in terms of prevention and treatment regimens).

The insufficiency of incentives assumption leads me to a research approach grounded mostly, but not exclusively, in the science of economics, dealing fundamentally with the question of the problem of incentives. That is, if eradication is possible, why hasn't it been achieved? And if elimination in most Sub-Saharan countries were possible, why hasn't it been achieved? Why do we *choose* not to eradicate malaria, and what factors influence those choices?

To bring the problem definition back to a more concrete space, let us return from the problem of malaria to what this dissertation does and does not do. Having defined the problem of malaria as one of sufficient means but insufficient incentives, my research focuses on the economic questions surrounding malaria control, elimination, and eradication at both the individual, firm, and societal levels with a particular interest in quantifying the costs of health interventions and their effects. It also takes a multi-stakeholder perspective and will explore the disconnect between what people say and what they do, among both those who research and those who are researched, since this disconnect fundamentally informs and misinforms our understanding of the malaria problem.

This dissertation does *not* “solve” the problem that it defines (the insufficiency of incentives for aggressive malaria control, national elimination, or global eradication), nor does it even aim to. On the contrary, in line with the “recursive” principles of both transdisciplinary research and “wicked problem” strategy research, this dissertation adopts the more modest mission of “shifting the goal of action on significant problems from ‘solution’ to ‘intervention’” (Knapp n.d.). In summary, if we accept the assumption that the component technical pieces of effective malaria control already exist, and therefore recognize that among the principle impediments to eradication are the insufficiency of incentives, our problem definition is not the resolution of those insufficiencies, but rather the identification of those incentives. And identifying incentives requires a quantification of factors involved, which brings us to the specific research aims of this dissertation.

1.2 Research aims

The general aim of this research is to gain insight into incentives for and against malaria control and elimination by (a) exploring unexploited partnerships with atypical stakeholders in malaria control through a quantification of costs and benefits of engaging in malaria control activities; (b) assessing uncertainty in regards to the cost of control and elimination-related interventions; (c) calculating the likelihood and time-scale to eradication,

as well as facilitating factors and barriers; and (d) assessing the reliability of some of the data we use to gauge control-related activities.

2. Theoretical background and framework

Any analysis which seeks to generate knowledge regarding health or economic behaviors requires a clear theoretical understanding of the reasons the decisions resulting in those behaviors are made. Investment in health – either at the individual level through health-seeking prevention methods such as sleeping under a bednet, or at the collective level through investment in measures which improve the health of a firm’s workforce – is not taken lightly by anyone who carries it out. On the contrary, the temporal nature of investment in its most broad sense (an up-front cost for a later payout) requires the incorporation of concepts like cost of capital, discounting, opportunity cost, and risk.

2.1 Human capital theory

Perhaps the most obvious starting point for a theory of what determines investment and behaviors in malaria-related activities is the canonical paper by Michael (Grossman 1972) in which he argues that health is itself a depreciating asset which can be increased by investment. This self-investment model, largely the foundation for the human capital theory insofar as it is applied to health economics, could be largely extrapolated to firms’ behaviors. However, Grossman’s focus is primarily at the micro-level, and because of this focus on the individual, he reduces complex systems of poverty (inherent to any analysis of malaria) to person-level variables such as individual education. In other words, while Grossman’s theory of health capital is not necessarily incompatible with a systemic analysis of the factors which influence malaria-related decisions, it is at least incomplete.

More contemporary theories offer more nuanced approaches. Abel expands Grossman’s somewhat reductionist approach to investing in health to incorporate cultural elements and normative beliefs, which transcend spectrums like education (Abel 2008). Many others have also expanded definitions outwards, terming concepts like “symbolic capital” to account for the extent to which the narrow-visioned understanding of capital as “money” from the Grossman area failed to explain why people engage in many health-related behaviors that have no financial or explicit biological “return on investment” (Schneider-Kamp 2020). Though more nuanced, contemporary theories are not so much a departure from Grossman than a re-casting of capital theory into a slightly more refined version of itself.

Though incomplete, human capital theory remains the most compelling theoretical framework for understanding the interplay between health and wealth insofar as decisions are made. For this dissertation, I assume those basic arguments of Grossman that (a) one can self-invest in health as a form of capital; (b) the return on that investment in its most basic form is production in the unit of health time; and (c) that health can also be an end unto itself (i.e., not “converted” back in to capital-producing production hours). That said, I go beyond Grossman’s initial theory in that (d) I put emphasis on the collective nature of health-related decision-making (as opposed to a individual model), and (e) I strive to incorporate economic resources not only as “environmental variables” which the individual can adjust to his or her liking, but as true constraints which bound decision sets in unique

ways over both space and time. In other words, scarcity sets real boundaries on investment decisions, both for individuals and organizations.

In addition to this variation on human capital theory, this research broadly incorporates the perspective of two further theoretical frameworks: (1) rational choice theory, and (2) the social-ecological model (SEM). The former provides the grounding on which we understand the inherent rationale behind individuals' and firms' decisions in regards to malaria-reducing activities, whereas the latter allows for an understanding of the factors which influence those decisions (i.e., why an investor chooses to spend money on malaria control activities, or why a villager chooses to sleep under a bednet).

2.2 Rational choice theory

Rational choice theory is the straightforward perspective of individuals maximizing their utility based on a consistent criterion and a limited options set (Eriksson 2011). Utility maximization is useful at the micro-level (in understanding why, for example, a person chooses to sleep under a net or answer a question in a certain way), but also at a macro-level (for understanding why and under what conditions firms invest in the health of their workers, countries in the health of their citizens, and supranational funders in the health agencies of countries).

Rational choice theory underlies most economic studies, and plays an important role in each of this dissertation's studies. However, beyond the specifics of each research question and the underlying assumptions in the methods used to address those questions, rational choice theory also plays an important role in the overall structure of this dissertation. As mentioned, my ingoing assumption towards the problem of malaria control is not an inadequacy of methods (the technical solutions for controlling malaria exist already, and the funding is arguably available), but rather an insufficiency of incentives.

Examining this insufficiency cannot be carried out at only one-level. At the macro-level, there is more than ample evidence that the benefits of malaria eradication would outweigh its costs (Sachs and Malaney 2002). At the micro-level, however, the utility of anti-malaria interventions is constrained by the options set (i.e., someone who is hungry may get more utility from a bednet as a fishing net); whereas once we mix levels, the incentives begin to become more complex and difficult to define. For example, a private firm may recognize that controlling malaria maximizes its own utility, but it may also be cognizant that by not engaging in malaria control activities, the government might step in and finance them. The interactions between these systems is why the theoretical framework of this study understands rational choice to be embedded *within* the social-ecological model, rather than a competing or separate framework.

2.3 Social-ecological model

Rationale choices do not exist in a vacuum; they are bounded by situational elements over which the chooser has varying degrees of control. The social-ecological model posits that individuals and environments exist in a complex, interactive system, and cannot be examined in isolation without a consideration of both their underlying and overlying

components (Golden and Earp 2012). It is a natural fit for transdisciplinary research insofar as it seeks to break out of narrow discipline scopes by understanding multiple levels of influence and interplay: the individual, the interpersonal, the organization, and the community (Bronfenbrenner 2000). It also fits well with the nature of this research in that it incorporates bi-directional causality; that is, it understands micro-systems as subject to the conditions of their multiple levels. To make this relevance more concrete, consider the nature of the act of sleeping under a bednet: it is conditioned by the family's ability to purchase or receive a net (micro), the society's aversion to or acceptance of nets (meso), the country's health budget or the amount of malaria-specific aid it received (exo), and the general research and funding climate on malaria elimination and eradication (macro). By the same token, each of the aforementioned systems exercises reverse influence as well. The general research and funding climate for malaria (macro) changes in light of national-level "successes" or "failures" (exo), which in turn are determined by how society perceives and relates to malaria control interventions (meso), which are themselves subject to whether an individual sleeps under a bednet or not (micro). A highly stylized example of these factors is in figure 1.3.

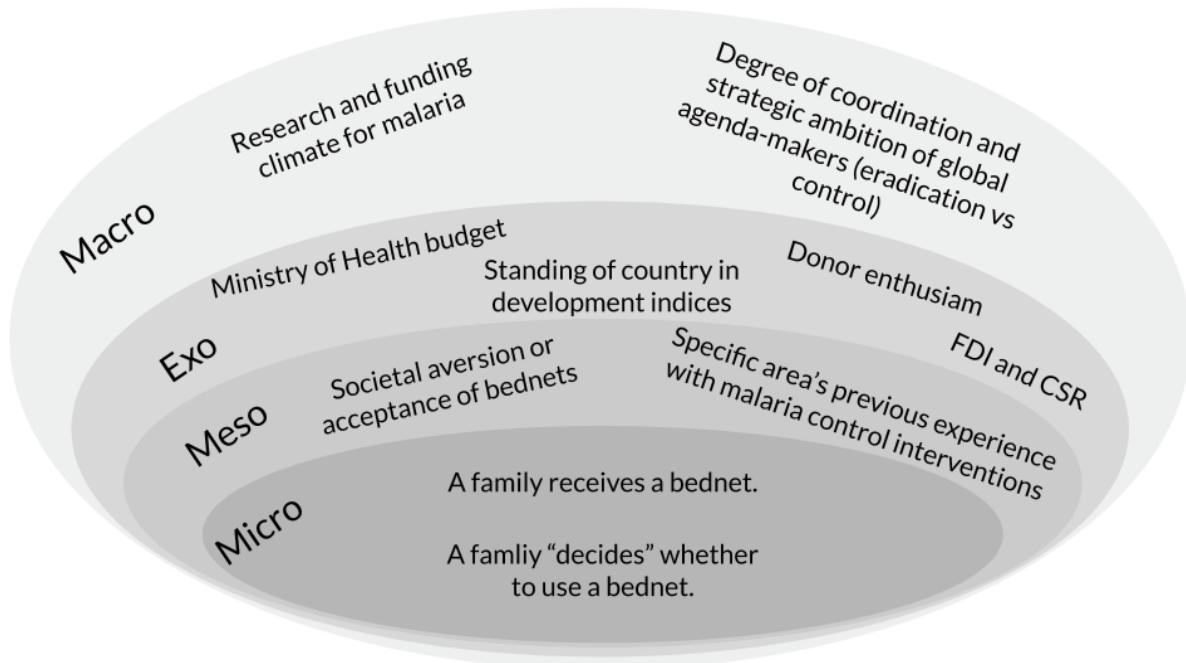


Figure 1.3: Example of the interplay of multi-level factors in a family's "decision" to use a bednet.

The social-ecological model is particularly relevant to my research into unexplored opportunities for collaboration with the private sector as well unexplored opportunities for health interventions. Taking a perspective which sees malaria not as a medical problem, but rather a problem at a myriad of levels (individuals, societies, countries, etc.) lends itself to stumbling upon the insight that malaria is also a problem for the private sector. In other words, with a social-ecological perspective on the private sector's role in malaria control is one that recognizes firms as "stakeholders" unto their own right, in the sense that they can be both beneficiaries of the public good of malaria control as well as contributors to it. Seeing the private sector as an equal stakeholder and potential partner in control also lends to identifying them not only as knowledge recipients (the typical stance of academia), but also knowledge generators; after all, many firms carry out malaria control activities during a

far longer period than the typical study protocol would permit (and thereby acquire significant amounts of knowledge).

The social-ecological perspective on the problem of malaria also helps to nudge one towards atypical solutions, and peripheral models. For example, if one accepts that the causes of malaria are not strictly biomedical (i.e., the usual academic definition of infection by parasite via vector), one naturally begins to look for solutions which are not located on that strictly biomedical causal pathway, but rather part of the epidemiological triangle (Gulis and Fujino 2015). This mindset, in essence, is what drives forward feasibility studies about interventions which have not yet taken place. These exercises in quantifying the benefits and costs of hypothetical future scenarios require an understanding of causal pathways which is not limited to viewing malaria as a strictly biomedical, individual-level, domain-specific problem. Quantifying the costs of a not yet invented vaccine and identifying ways to optimize the roll-out of a not yet proven antiparasitic drug requires “moving beyond parochial perspectives” (Aguirre et al. 2019).

2.4 Reconciling multiple frameworks

Utility maximization – the core tenant of rational choice theory – is assumed in all studies, and fits squarely within human capital theory. In fact, one could make the case that human capital theory is itself an attempt to reconcile traditional theories around capital-seeking behaviors with economics’ inability to understand health-seeking behaviors. Both rational choice and human capital theory would present decisions around eradication-related investments as potentially “solvable” insofar as one could estimate the correct parameters for each actors’ utility functions and health expectations.

It may appear, however, that these two frameworks are at odds with the social-ecological model. After all, the social-ecological model for behavior emphasizes complex associations in its explanation of behaviors, whereas rational choice theory reduces these complex associations to one utility function. This dissertation does not resolve this tension, nor does it strive to. Rather, it attempts to live within the tension, seeking to understand the landscape of malaria economics through that of rational actors living in a complex social-ecological environment. In other words, my conception of these theories, and my implementation of them into my research is one of containment: I understand individuals and firms to be rational, utility-maximizing actors (rational choice theory) existing in a complex, interactive environment with multiple, dynamic levels (social-ecological model).

3. Research Design

3.1 Research questions

The general research question driving this dissertation is: what are the incentives for and against malaria control activities?

The specific-questions are:

1. Where do opportunities exist for enlarging the body of stakeholders and funders involved in malaria control?
2. What is the likelihood of and time-frame to malaria eradication?
3. How much does malaria control cost?
4. What are the effects of malaria control and elimination activities?
5. To what extent can we rely on the data generated by malaria-related research?

The questions are addressed in six studies. The extent to which each study responds to these questions is viewable in table 1.

Table 1. Research questions addressed by each study (small x = tangentially addressed)

Research questions	Study number					
	1	2	3	4	5	6
Where do opportunities exist for enlarging the body of stakeholders involved in malaria control?		X			X	X
What is the likelihood of and time-frame to malaria eradication?	X					
How much does malaria control cost?				X		X
What are the effects of malaria control and elimination activities?			x			X

To what extent can we rely on the data generated by malaria-related research?	x		x	x		
-------------------------------------------------------------------------------	---	--	---	---	--	--

3.2 Hypotheses

The ingoing, cross-cutting hypothesis to these research questions is that there exists an insufficiency of incentives for individuals and firms to invest meaningfully in malaria control and elimination measures. As with traditional laboratory research, I set out to disprove this null hypothesis by gathering evidence regarding malaria-related behaviors at both the individual and firm level, as well as perceptions regarding the utility of research data and feasibility of achieving eradication. This body evidence was formed with the following specific hypotheses in mind (each one pairable with its respective research question):

1. Significant opportunities for enlarging the body of stakeholders and funders involved in malaria control do not exist, because the economic incentives for scaled-up control efforts are not sufficient.
2. The likelihood of and time-frame to global malaria eradication, as perceived by malaria researchers, is lower and longer than institutional discourse would suggest; this gap can be explained by the need for institutions to project optimism in order to attract funding, and the hesitance of researchers to express pessimism for reasons of social desirability bias.
3. Malaria control is prohibitively expensive in many contexts, making scaled-up control (elimination efforts) economically unfeasible.
4. The economic effects of malaria control activities and interventions are positive, but not sufficiently sized to offset the financial costs.
5. The health effects of malaria control activities may be less than what researchers perceive via the biased data which they collect; this gap between reality and registration could partially explain the historical failure of eradication campaigns and the current stall in progress.

3.3 Research approach

This research was carried in the framework of “emergent design” (Schneider-Kamp 2020; Cavallo 2000). That is, the studies were not conceived in their entirety *a priori*, but rather emerged sequentially as results were generated and knowledge was acquired. As is typical in emergent design, the process of answering one research question satisfactorily required making assumptions, which in turn lead to more research questions. Though unstructured, the advantage of an emergent approach in this dissertation was that it allowed for the unanticipated information to find its way into the hypotheses generating and testing processes.

At a high-level, the research follows three cores themes:

First, I examine the role of the private sector in malaria control: that is, given that the public sector has not yet achieved the public good, which would be malaria eradication (even with some noteworthy collaborations with the private sector, such as the malaria vaccine), I explore the incentives for and impediments to the private, for profit, non-health sector scaling up their involvement in anti-malaria activities (“Foreign Direct investment, corporate social responsibility, and malaria control in Mozambique - trends, risks, and opportunities”), cognizant both that firms will be in large part the beneficiaries of control, but an overreliance on them creates a potentially unacceptable risk for society. In this same line, I go from macro (firms) to micro, carrying out an in-depth examination of one Mozambican sugarcane facility’s absenteeism, clinical, and fumigations data so as to understand whether malaria control was “profitable” or simply socially “good” (“Is malaria control profitable? Return on investment of residential fumigation at a sugarcane processing facility”).

Second, I seek to understand if the information systems researchers use for monitoring malaria interventions are themselves flawed: that is, perhaps we are mismeasuring the *inputs* of malaria control initiatives, and this mismeasurement could explain, at least to some extent, why the *outputs* of these initiatives have been disappointing. In this line of research, I examine whether bednet usage reporting might be tarnished by social desirability bias (“Evidence of high bednet usage from a list randomization in rural Gambia”).

Third and finally, I seek novel data sources that allow for envisioning both how and when malaria eradication might be achieved. In this line of work, I elicit and aggregate views on eradication from 1,000 malaria experts (“Researchers’ perceptions of malaria eradication: findings from a mixed-methods analysis of a large online survey”), identify opportunities where non-traditional cross-species interventions might be most effective (“Mapping the potential use of endectocide-treated cattle to reduce malaria transmission”), and quantify the roll-out costs of a hypothetical future malaria vaccine in Sub-Saharan Africa (“A systematic review of the incremental costs of implementing a new vaccine in the expanded program of immunization in Sub-Saharan Africa”).

The below schema reflects a complex process distilled to its core components.

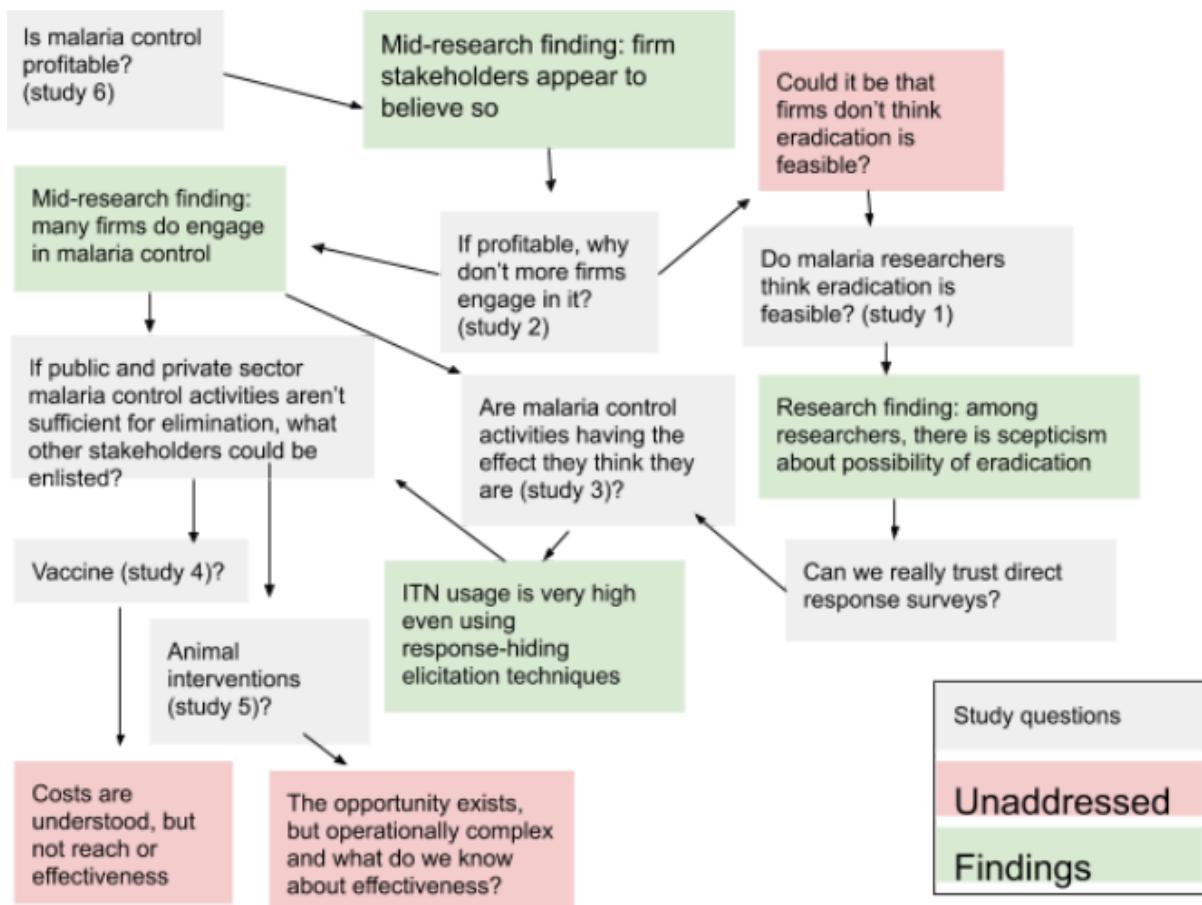


Figure 1.4: Rough overview of the “emergent design” approach of this PhD: questions leading to answers leading to questions, and so on.

3.4 Studies

The research of the thesis comprises six studies, which are each briefly presented below.

Study 1 – Researchers’ perceptions of malaria eradication: findings from a mixed-methods analysis of a large online survey – sought to estimate the probability of, and time-frame to, global malaria eradication given researchers’ perceptions on the matter. We carried out a large ($n=844$) online survey of peer-reviewed malaria researchers from a myriad of backgrounds, asking both quantitative and qualitative questions on when and whether eradication would occur, and what obstacles stood in the way. This was a mixed-methods study using both closed- and open-form questions. Analysis was both quantitative and qualitative. We found that researchers were more pessimistic than the position generally taken by institutional discourse, and explored implications for the expected value of the returns on eradication-specific investment.

Study 2 – Foreign direct investment, corporate social responsibility, and malaria control in Mozambique - trends, risks, and opportunities – aimed to explore the role of the private sector in malaria control in Mozambique. This was a mixed-methods study. Carrying out an analysis of publicly available datasets, and a systematic review of both grey

and academic literature pertaining to foreign direct investment and corporate social responsibility in Mozambique, we analyzed the issues and trends associated with the private sector's role in malaria control, and explored opportunities and risks for malaria elimination in the context of the private sector delivering a public good.

Study 3 – Evidence of high bednet usage from a list randomization in rural Gambia – employed a list randomization experiment to partially obscure respondents' answers to questions pertaining to bednet usage, so as to arrive at an estimate of true bednet usage with less social desirability bias. This was a survey of 196 participants carried out within the context of a larger randomized trial. We found that, even with the de-biasing method, estimates for bednet coverage were very high.

Study 4 – A systematic review of the incremental costs of implementing a new vaccine in the expanded program of immunization in Sub-Saharan Africa – combined data from a myriad of vaccine studies and programs in Sub-Saharan Africa in an effort to estimate the incremental cost of a hypothetical malaria vaccine. This was a traditional systematic review, albeit with a more developed quantitative component than most. Though we were able to generate an estimate for operational planning purposes, we found costs across programs to be hugely variable.

Study 5 – Mapping the potential use of endectocide-treated cattle to reduce malaria transmission – used publicly available data to identify a potential elimination opportunity than a non-traditional method; endectocide in livestock for malaria control. This was a spatial data analysis study. We found that the benefit of such a program would be highest in West Africa, where the prevalence of malaria among children, the density of partly zoophilic malaria vectors, and the density of cattle coincides to a large degree.

Study 6 – Is malaria control profitable? Return on investment of residential fumigation at a sugarcane processing facility – was an in-depth examination of the administrative data of a sugar mill in southern Mozambique. This was a retrospective return on investment study. Using absenteeism, clinical, weather, and fumigations data, we estimated both the costs and effects of the company's malaria control program, and quantified return on investment. Our results showed that, from a purely financial perspective, the program was profitable.

3.5 Ethics

Study 1 was given an exemption from the Scientific Committee of ISGlobal given that it did not deal with any health data. Study 2 used only publicly available data and involved no human subjects. Study 3 was carried out in the context of a larger housing improvement study. It was approved by the Gambia Government and Medical Research Council's joint ethics committee. Study 4 involved no human subject data. Study 5 used only publicly available data and involved no human subjects. Study 6 was approved by the Institutional Ethics Review Board for Health the Centro de Investigação em Saúde de Manhiça (CIBS) prior to data collection.

4. Study 1: Researchers' perceptions of malaria eradication: findings from a mixed-methods analysis of a large online survey

RESEARCH

Open Access



Researchers' perceptions of malaria eradication: findings from a mixed-methods analysis of a large online survey

Joe Brew^{1,2*} Menno Pradhan^{2,3}, Jacqueline Broerse² and Quique Bassat^{1,4,5,6,7}

Abstract

Background: The value of malaria eradication, the permanent reduction to zero of the worldwide incidence of malaria infection caused by human malaria parasites, would be enormous. However, the expected value of an investment in an intended, but uncertain, outcome hinges on the probability of, and time until, its fulfilment. Though the long-term benefits of global malaria eradication promise to be large, the upfront costs and uncertainty regarding feasibility and timeframe make it difficult for policymakers and researchers to forecast the return on investment.

Methods: A large online survey of 844 peer-reviewed malaria researchers of different scientific backgrounds administered in order to estimate the probability and time frame of eradication. Adjustments were made for potential selection bias, and thematic analysis of free text comments was carried out.

Results: The average perceived likelihood of global eradication among malaria researchers approximates the number of years into the future: approximately 10% of researchers believe that eradication will occur in the next 10 years, 30% believe it will occur in the next 30 years, and half believe eradication will require 50 years or more. Researchers who gave free form comments highlighted systemic challenges and the need for innovation as chief among obstacles to achieving global malaria eradication.

Conclusions: The findings highlight the difficulty and complexity of malaria eradication, and can be used in prospective cost–benefit analyses to inform stakeholders regarding the likely return on eradication-specific investments.

Keywords: Malaria, Eradication, Elimination, Mixed methods, Survey, Crowdsourcing, Probability, Opportunity cost

Background

Malaria is a parasitic disease transmitted among humans by mosquitoes. *Plasmodium falciparum* accounts for many of the 200 million annual cases as well as most of the half million annual deaths worldwide [1, 2]. Malaria “elimination”, the “interruption of all local transmission of the infection in a country or region” [3] is actively being pursued by dozens of countries around the world, leading to a renewed push for “eradication” (“the permanent

reduction to zero of the worldwide incidence of malaria infection caused by all species of human malaria parasites”) [4]. The rationale for pursuing eradication is straightforward: the annual burden of malaria is so high that eradication is simply “necessary” [5]. With this renewed push has come renewed debate on whether a time frame is a realistic or desirable component of eradication [4].

This is not the first time that malaria eradication has been in the international spotlight. The scientific and public health communities have had eradication on their policy agenda since the World Health Organization (WHO) established the Global Malaria Eradication Programme in the 1950s [6]. In 1957, U.S. President Dwight

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Eisenhower told Congress that malaria could be expected to be eradicated in five years. Despite an “extraordinary sense of international purpose”, the top-down and one-size-fits-all campaign which followed did not achieve its goal [7]. Following the failure of the WHO’s first attempt, the focus shifted away from global eradication towards local control strategies, though the goal of global eradication was never formally abandoned. The change in strategy from global eradication to local control had the effect of less interest and funding for aggressive anti-malarial interventions, leading to an increase in malaria’s burden. In recent years, much of the discourse regarding malaria has shifted back to global eradication [8], with funders, researchers, and public health practitioners rallying to the cause [3]. The Bill and Melinda Gates Foundation began actively promoting eradication beginning in 2007, and in recent years has described eradication as feasible “within a generation” [9]. The WHO also set ambitious goals, stating the objective of eliminating malaria in 35 new endemic countries from 2015 through 2030, and reducing all deaths from malaria by 90% [10]. Progress towards elimination and eradication efforts slowed, however, towards the end of the decade. The WHO Strategic Advisory Group on Malaria Eradication acknowledged “stalling progress” and that meeting the 2015 targets was “unlikely” [11]. Meanwhile, the Lancet Commission argued that global eradication by 2050 was both a “necessary” and “attainable goal” [5].

From both policy [12] and scientific [13] points of view, eradication has never before received so much attention. Prior to the Lancet Commission, most recent research on expert opinion regarding the feasibility of malaria eradication focused on the *how* rather than the *if* and *when* [3]. International programmes, such as the WHO Global Malaria Programme (GMP), have acknowledged the need “to take an official position on how and under what timeline malaria eradication could be achieved” [14]. The Lancet Commission did just this, setting 2050 as the mark. However, the WHO Strategic Advisory Group on Malaria Eradication argued that “eradication by a specific date is not a promise we can make” [11]. In other words, there seems to be universal consensus among experts regarding the desirability of global eradication, but discord on the timeline and feasibility.

Clarity on timeline and likelihood of eradication could inform forecasting of disease transmission, and plays a crucial role in the economic analysis of the expected value of malaria eradication initiatives, ultimately informing health policy decisions. But achieving clarity is difficult, given the many complex and interacting variables, which affect malaria transmission, research funding, and technological development. The lack of a clear scientific consensus regarding the timeline to and probability

of eradication can be considered an important knowledge gap with real consequences: not knowing an “investment’s” maturity date or risk profile is a deterrent to any “investor” (public or private) in the public good of malaria eradication. In other words, funding for eradication-oriented interventions could potentially be greater if funders perceived less uncertainty. Similarly, policy-makers in resource-scarce contexts must weigh the hypothetical benefits of a costly intervention against the risk of the intervention’s intended outcome not occurring; having more clarity on eradication’s timeline and likelihood could inform these decision-making processes.

The general objective of eradication serves to inspire, rally funder support, motivate researchers, and focus the efforts of public health practitioners. To the extent that malaria eradication (by definition) has never occurred, the parameters needed for an ex post cost–benefit analysis are unknown. Nonetheless, prospectively estimating eradication’s return on investment is crucial to deciding when and how to pursue the goal, especially in light of the high direct and opportunity costs of eradication-specific interventions. One approach to economic evaluation is the use of infectious disease transmission models. These have been applied to diseases which are closer to eradication than malaria, since the uncertainty around model input parameters is less, requiring fewer cascading assumptions in order to present possible comparative scenarios. For example, Kastner et al. were able to describe 4 relatively realistic pathways to lymphatic filariasis eradication, as well as the pre-requisite role and magnitude of certain interventions [15]. A similar modelling framework was then used to estimate the cost of eradication [16]. A recent modelling analysis on onchocerciasis eradication, based on a disease transmission model, showed that the costs of elimination (relative to staying in “control mode”) in Africa would be far lower even in the short term, thanks to the improvements it would lead to in both treatment times and prevented surveillance costs. Given the relative proximity of eradication, and the narrow geographic scope, the authors were also able to estimate the timeline to eradication [17].

This level of detail and specificity in the economic evaluation landscape of malaria eradication, unfortunately, is not possible, given its high prevalence and epidemiological complexity. In fact, there are no transmission models estimating the likelihood and time frame of eradication, or its derivative cost–benefit ratio. Globally, where transmission modelling has been used for the purposes of forecasting the future epidemiology of malaria, the methods have generally been aimed at optimizing elimination methods, determining whether a strategy is scalable [18], guiding funding and drug development [19, 20], or comparing a range

of hypothetical morbidity scenarios [21], rather than assessing the likelihood of or time until the occurrence of eradication.

To the extent that estimating eradication's likelihood and timeframe is essential to forecasting the cost-benefit ratio of eradication interventions, alternative methods are needed to forecast such parameters. Just as the stock market aggregates perceptions to provide an assessment of something as complex as a company's value, aggregating perceptions may be a useful tool for tackling the complexity of malaria eradication. Many studies have shown value in expert elicitation as a means to reduce uncertainty and inform decision-making [22], and various techniques—such as the well-known Delphi Technique—exist to generate consensus from multiple points of view [23]. As Francis Galton demonstrated in his famous study in which he showed that the crowds' aggregated estimates of cow's weight formed a quasi-normal distribution centred around the true weight [24, 25], averaging the perceptions of many can be more accurate than taking the opinion of any single expert, since the biases of diverse viewpoints can be complementary and symbiotic. Measuring consensus and discord among disease-specific researchers from a variety of disciplines can serve as a barometer of (informed) opinion, both guiding resources and identifying areas of concern [26].

The optimal assignment of resources for malaria eradication campaigns hinges on the expected value of those campaigns, the latter being a direct function of the discounting applied to future benefits and the probability of "success" (i.e., eradication). Holding constant factors such as the cost of eradication and the benefits of achieving it, the return on investment of malaria eradication initiatives is a function of eradication's timeframe (assuming a >0 discount rate) and probability (assuming a $<100\%$ likelihood of success). Given this, estimating these parameters is crucial to evaluating if and when attempts at eradication should be undertaken.

The aggregation of malaria researchers' perceptions regarding the time frame and likelihood of eradication can be understood to form a probability distribution, which can be used to estimate the expected value of eradication-specific investments. The objective of this study is to gauge (expert) opinion about, estimate the likelihood of, and quantify the potential time frame to malaria eradication through a systematic online survey of malaria research professionals from a wide array of academic disciplines. Doing so may guide the optimal distribution of health resources by informing estimations of the expected value of malaria eradication efforts.

Methods

The study population included all first authors (with available email addresses) returned in a PubMed search for the term "malaria" from January 1, 2010 through December 20, 2016. PubMed was used because it was the most comprehensive publication database for malaria-related research, and also exposed enough metadata about articles and authors so as to allow for relevant analysis. Personalized emails addressing the author by name and mentioning the relevant paper were sent to each of the 7680 authors during the period from December 20, 2016 through January 2, 2017. Researchers were invited to participate by clicking a link to the survey form. The survey was simple, consisting of only name, email, and four content-related fields along with a "general comments" section.

Content-related survey fields consisted of:

1. Area of expertise.
2. Perceived probability (%) of malaria eradication in 10, 20, 30, 40, and 50 years.
3. Free choice perceived number of years until malaria eradication.

The survey was intentionally as short as possible, so as to appeal to time-pressed participants. However, supplementary data on researchers is useful for the assessment of selection bias and determinants of perception, we estimated participant gender, total number of citations, and total number of peer-reviewed articles published. In order to estimate whether a user was male or female, data were used from the North Atlantic Population Project, and U.S. government [27]. Total citations and total publications were binned into three categories: 0–5 (junior-level researchers, PhD students); 6–99 (most professional academics); and >99 (the most prolific researchers). The searching and retrieval of information pertaining to articles and citations from the PubMed database was carried out using tools from the RISmed package [28]. Citations and publications outside of the PubMed database were not captured. Information retrieved about authors was used to de-bias parameters in an ordinary least squares regression, analysing the association between number of publications and perceived years to eradication.

Survey results were first analysed descriptively. Following Galton's example [25], point estimates for event probabilities were estimated as the average of all responses, and the totality of the responses to each numeric question were used to estimate uncertainty around those likelihoods and time frames.

Quantitative analysis was carried out in R language (R Core Team, 2015). Qualitative analysis of free text comments was carried out using thematic analysis, with

inductive open coding carried out iteratively [29]. In the final, open-ended question, participants were invited to provide “any general comments on the timeline and likelihood of global eradication”. Thematic analysis [30] was employed to code responses following the 6-phase approach laid out by Braun and Clarke [31]. The approach underwent several iterations in which codes were modified, discarded and created. One coder carried out all thematic coding and classification; quality control was assured through multiple, iterative reviews with the authorship team. Using the RQDA software to assist in data management and theme coding [32], four subject themes were identified. Comments were additionally coded as either descriptive (comments pertaining to the “problem” of malaria eradication) or prescriptive (pertaining to potential “solutions” for eradicating malaria). Finally, free-text comments were scored for overall sentiment polarity [33].

Results

Participant characteristics

A total of 884 researchers participated in the survey from the 7918 invitations sent (participation rate of 11.2%). Areas of expertise were non-exclusive and self-described, with participants having the option to choose from up to 3 of 10 checkboxes, or to write in one or more “other” areas of expertise. 604 (68.3%) participants declared at least one area of expertise.

Participants had a total of 219 unique (self-described) areas of expertise. The five most popular were Epidemiology (357), Information Technology (344), Parasitology (319), Biology (277), Clinical medicine (207) (see Table 1).

Respondents were qualitatively different from non-respondents. Importantly, the average number of total author-specific citations was 40.9 among respondents, but 92.9 among non-respondents. When examining the number of average citations per article, the difference between respondents remained: 4.8 among respondents, and 9.0 among non-respondents, highlighting the greater impact of non-respondents relative to respondents. Males responded at a greater rate (12.2) than females (9.1).

Perceptions of likelihood of eradication

Most participants saw eradication as extremely unlikely in the next 10–30 years, but increasingly likely thereafter. Figure 1 shows the distribution of year-specific likelihood perceptions (panels A–E), as well as an illustration of how both likelihood and uncertainty grow over time (panel F). At the 40-year mark, the distribution of perceived likelihood of eradication appears “normal”, and by 50 years it is slightly shifted to the right (i.e., consensus is towards eradication more probable than not).

Table 1 Sample size and average perceived years until eradication by area of expertise

Area of expertise	Average years	Number of participants
GIS	50	5
Infectious disease	50	7
Malaria	50	8
Medical entomology	49.09	12
Political science	48.75	14
Vector control	48.75	9
Drug discovery	48	5
Microbiology	48	5
Pharmacology	47.78	9
Anthropology	47	20
Economics	46.84	34
Public health	45.96	29
Entomology	45.84	58
IT	45.79	344
Parasitology	45.74	319
Biology	45.70	277
Virology	45.65	23
Clinical medicine	45.56	208
Epidemiology	45.31	357
Immunology	44.3	104
Bioinformatics	44	5
Statistics	43.73	86
Ecology	42.57	8
History	42.5	6
Pharmacy	42	5
Vector biology	41.6	5
Geography	40	5
Chemistry	37.46	27
Biochemistry	37	5
Medicinal chemistry	34.57	7

Values of more than 50 years or “never” were coded as 50 for the purpose of estimating averages

In regards to responses to perceived years until eradication, 59 (0.7%) were either blank or unintelligible, whereas 825 participants provided an estimated number of years. Three quarters of the respondents, 616 (74.7%) estimated that it would be 50 or more years until eradication. Differences were not significant between different areas of expertise (Table 2).

In order to de-bias sample selection, a simple binomial logistic regression model was estimated on the likelihood of response as a function of gender and (binned) number of citations. Having estimated the odds of survey participation, the inverse of the selection model’s predictions were employed as weights in a simple linear model to adjust estimates. A separate

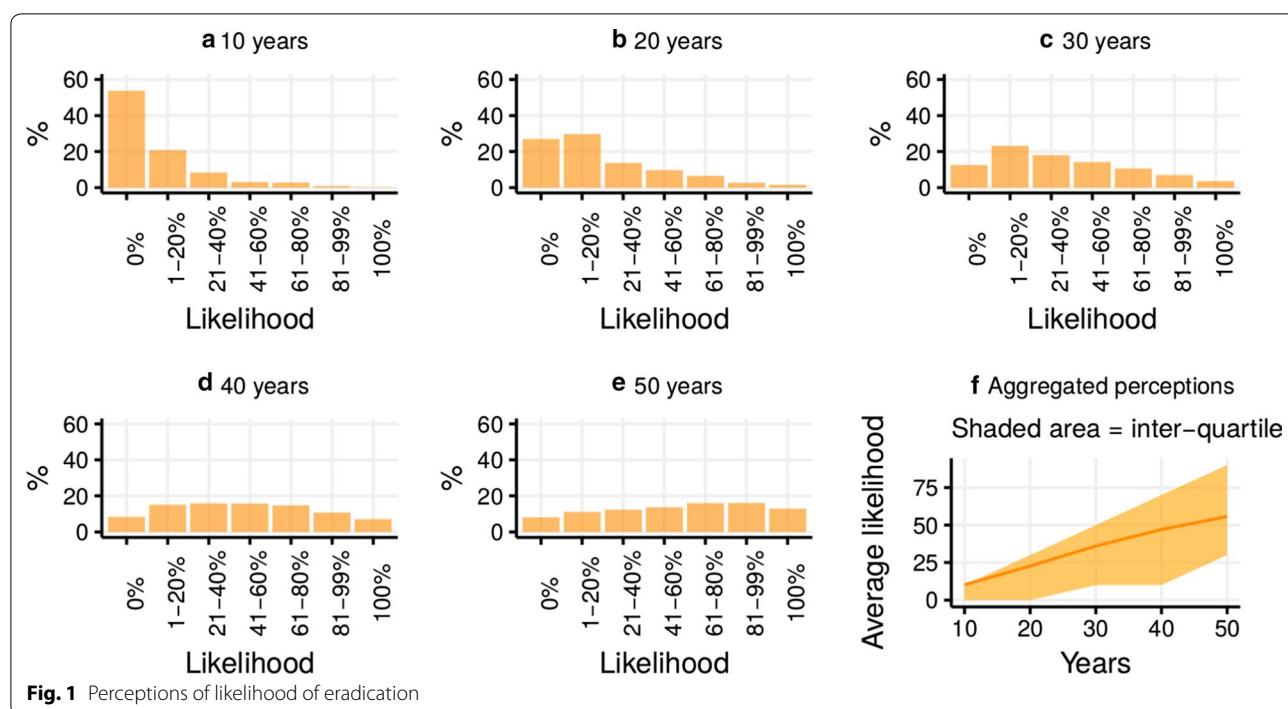
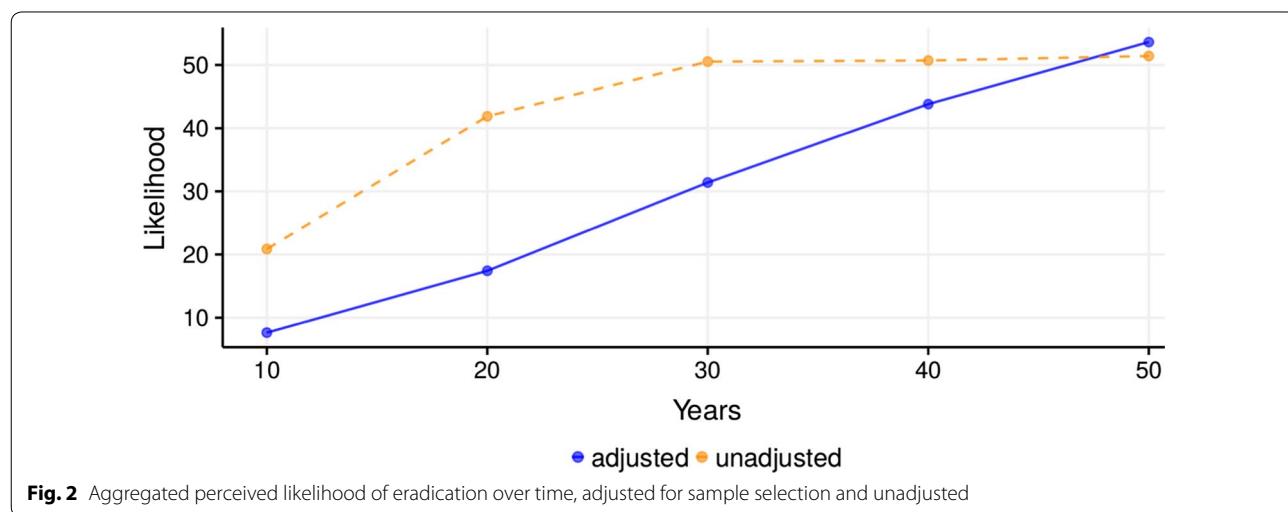


Table 2 Response rate by participant characteristics

Variable	Characteristic	Responded	Invited	Response rate (%)
Sex	Female	209	2287	9.1
	Male	358	2939	12.2
	Unknown	317	2692	11.8
Citations	0–5	621	3299	18.8
	6–99	179	3270	5.5
	> 99	84	1349	6.2

weighted model estimated the likelihood of eradication at 10, 20, 30, 40, and 50 years. Figure 2 shows both the aggregated perceived likelihood of eradication over time before and after adjusting for sample selection based on binned number of publications and gender. Adjusted and unadjusted estimates coincide in the long-term, but diverge sharply in the near-term; adjustment suggests that had the pool of respondents been more representative, the average perceived likelihood of near-term eradication would have been much lower.



Roughly, the adjusted perceived likelihood of eradication tracks the number of years into the future.

Perceptions of eradication's challenges and complexity

Of the 884 who responded to the survey, 540 (61.1%) provided a comment. Relative to non-commenters, commenters were more optimistic on average, but also more polarized in opinion. The three subject themes identified through the procedure of iterative, open coding were:

1. *Solutions*: Comments pertaining to the innovations required to achieve eradication, priorities, and the desirability of certain approaches.
2. *Systemic challenges*: comments pertaining to political, social, environmental or logistical issues related to eradication.
3. *Complexity*: comments which focus on the multi-dimensional components of eradication.

Comments were also classified as descriptive or prescriptive. A majority (59.3%) were descriptive. Descriptive commenters were more pessimistic (in regards to perceived years until eradication) than prescriptive commenters, though this difference did not reach the level of statistical significance ($p=0.21$, Pearson's Chi-square). Descriptive comments also received sentiment polarity scores which were more negative than prescriptive comments, although again this difference did not reach the level of statistical significance ($p=0.18$).

In regards to *solutions*, comments largely pertained to the necessity of further technological advances and innovations. One clinical epidemiologist wrote that "currently available technology can't achieve [eradication], even if delivered optimally"; a parasitologist argued that eradication could not be achieved without a "game-changing innovation", whereas multiple others referred to the need for "transformative" technologies:

We can't achieve eradication with our current tools. We'd need new medicines, a better vaccine, and maybe other vector control tools.

Many noted the need to "overcome the challenge of drug resistance". More than 10% of commenters noted the need for an effective vaccine. Genetic engineering was mentioned by several commenters as a promising means to achieve eradication quickly. Most comments coded as "solutions" were prescriptive in nature, often suggesting the nature of the needed innovation, with a heavy slant towards pharmaceutical options and vaccination.

Systemic challenges to malaria eradication were noted by the majority of commenters. Comments in this category can be divided into four sub-themes: (i) lack of coordination, (ii) lack of good surveillance and health services

delivery, (iii) lack of political will and (iv) poverty. In direct contrast to the previous comments, many echoed the comments of an epidemiologist who stated that "we already have the tools to achieve eradication" and that the only piece lacking was "robust health systems". Many commenters noted problems of coordination, as illustrated in the below quote from a biologist.

It will be very difficult to eradicate malaria... not because we don't have the technologies, which we already have... the problem is politics. Malaria doesn't stop in (sic) borders of a country and it would take a joint effort of a lot of political leaders to get programs in place to fight malaria. Unfortunately I don't see this happening anytime soon.

Others echoed the sentiment, with many comments focusing on the need for strong surveillance and treatment delivery systems. Many commenters focused on other reasons for stagnating progress; for example, a public health specialist pointed out the importance of "weak or failing health systems...due to political unwillingness or conflict". Many noted that malaria is a "disease of poverty", with "social injustice" as the root cause. Some made the sequential argument that "eradication of poverty" must precede disease eradication. Along the same lines, one epidemiologist wrote:

Eradication requires a full systems-wide approach, not a disease-specific approach. The eradication of smallpox was a triumph of management, not medicine or technology.

Another epidemiologist noted that the survey "left off the list the most important factor—economic development". Many echoed the sentiment, stating that without economic development, eradication will be impossible, and that poverty is the "cause" of malaria. Comments coded as "systemic" tended to be descriptive and more pessimistic than others.

Complexity was a relatively rare category (<20% of all comments), those whose comments were coded as the "complexity" category were more pessimistic than average in regards to the timeline and likelihood of eradication. Many commenters highlighted the inherent challenges in the epidemiology of malaria, such as the changing dynamics of malaria transmission, the resilience of the parasite and vector, climate change, and the inability to aim interventions accurately with an "ever-moving target". The potential for adaptation was highlighted in reference both to the mosquito as well as the parasite itself. Several participants pointed out that the vast animal reservoirs for *Plasmodium knowlesi* made it "impossible to eradicate". Many comments addressed the fact that the conversation on eradication is largely taking

place within the public health community, whereas the causes of malaria endemicity are largely orthogonal to public health interventions. Several commenters pointed out the multitude of prerequisite conditions for eradication to even be considered feasible; for example, an economist and statistician noted:

To my mind, this question is highly dependent on background context, e.g. global political and economic dynamics, as well as international conflict. Complete global eradication is an extremely singular goal that requires a vast array of necessary conditions - if any of these fail, eradication will not be achieved.

Many commenters thought that the terms "eradication" and "malaria" were so complex and nebulous that public health practitioners should avoid them all together, so as to not repeat the mistakes of the WHO GMP in the 1950s. For example, some implied that there were—at least operationally—multiple "malarias", and talking about "malaria" as one disease misses the mark, since the different species of parasite and contexts in which they live make elimination in each area very distinct from other areas. One clinician wrote that eradication is a "postwar" idea that developed from the "abandonment of a broad sociopolitical understanding of the causes of disease, and the emphasis on technological solutions." Many stated that global malaria eradication was simply not possible, and two argued that it may not be desirable or ethical. One epidemiologist stated that the concept was "absurd" and that "I'm not even sure why people talk about it". A clinician questioned the utility of discussing "eradication" as a concept:

Eradication is a different objective than elimination. Elimination means that the disease is not endemic but could reappear even in a country like Norway if infrastructure breaks down. Elimination may be possible in poor endemic countries, following socio-economic development. Eradication means that the parasite disappears from the planet, which is not realistic...

Comments questioning the utility of eradication as a concept or goal tended to be skeptical of its feasibility. Largely, they were prescriptive, advocating for a re-framing of the conversation so that the focus was not on an "arbitrary" goal like eradication, but rather on scaling up control and making region-specific progress.

Discussion

This study has elicited researchers' view, through an online survey, on likelihood and approximate time to malaria eradication. Roughly three-quarters of

respondents believe that malaria will not be eradicated in the next half century. When adjusted for selection bias, the perceived likelihood of eradication in 50 years remains similarly low, but estimates for shorter-term eradication are even lower.

Eradication of a disease is a "high stakes game", exposed to multiple competing—and at times contradictory—incentives from multiple stakeholders [34]. Understanding these incentives, and the factors which can alter them, is vital to anticipate how eradication can succeed, and the specific aspects where failure may be more likely. In fact, disease eradication is a typical example of public good, where free-riding can determine failure. Cooperation, collaboration, generation of incentives or potentially even impositions could represent solutions to the free-riding problem. Either in the absence or with not so stringent budget constraints limiting the investment, a high and certain return on investment could, by itself, constitute a key disincentive to free ride. However, the return on investment of eradication-specific interventions is affected by the fact that most researchers agree that eradication will take a long time to achieve. This, in turn, reduces the expected value of future benefits, disincentivizing eradication-specific investment. Given this, it is important to quantify the positive externalities of "failed" eradication, as well as the potential backfire effects. That is, the reduction in burden of disease can still make interventions worthwhile, but an abandonment of efforts if ambitious goals are not met may lead to resurgence in malaria as was the case in the 1970s following the GMEP's failure at eradication. This study did not endeavour to make this quantification.

However, areas of high malaria endemicity are often also those with high competing health costs. When estimating the return on investment of malaria elimination initiatives, not only must one take into account the potential benefits (even in the case of failure), but also the opportunity costs (even in the case of success). After all, eradication and elimination are not binary success/failure propositions—an initiative should be judged both on its epidemiological circumstances [35] as well as the counterfactual improvements in health which could have been achieved via other paths. Even if one considers malaria eradication to be as utopic as "world peace", it might still have utility (in terms of generating political momentum and mobilizing resources), as well as risks.

Limitations

This paper has several limitations. Conceptually, academic researchers are specialists—their narrow, field-specific view of eradication's feasibility is of arguable reliability, given that they may be unfamiliar with the operational, cultural and "real-world" challenges of

malaria eradication. Though crowds have been found to be more “wise” than individuals in many cases, the application of an approach similar to the “wisdom of crowds” is not suitable to all classes of problems [36]. Crowds can be susceptible to social biases [37] (although this survey’s anonymity largely protects against this issue), and other biases may come in to play, especially given that our study was of a crowd of “specialists” (from only one publication database), rather than the population as a whole.

Though sample size was large, response rates were low, calling for the need to address potential selection bias. In the case of gender, even though males responded at a significantly greater rate than females ($p < 0.001$, Pearson’s Chi-squared), selection bias was not of concern since there were not significant differences by gender in regards to pessimism/optimism (ie, time frame or likelihood of eradication). In the case of researcher impact (as measured by the total number of citations), selection bias plays an important role: being highly-cited was associated both with eradication “pessimism” as well as likelihood of non-response. In other words, the pool of respondents was less highly-cited than the pool of invitees, and among respondents, those who were highly-cited tended to be more pessimistic. Though results were de-biased, selection bias on other (unobserved) variables may still exist.

Three additional potential biases are worth mentioning specifically. (1) “Conjunction fallacy” suggests that the general goal of eradication may seem less likely than the aggregation of the goals of country-specific elimination. (2) A (reverse) variant of the “hot hand fallacy”, in which researchers may mistakenly base their assessment of current chances of eradication on previous failures. (3) Parkinson’s law of triviality suggests that researchers may disproportionately see the challenges of their own research (e.g. anti-malarial drug resistance) as larger or more relevant to the global eradication campaign than they really are.

As with the survey of experts of Keenan et al., regarding the feasibility of eradication of neglected tropical diseases, this study detected relatively high levels of eradication skepticism and did not delve into whether researchers had clinical or operational experience, nor did it assess opinions of program workers, nor did it explore complexities pertaining to different types of or forms of existence of malaria. Though this study’s sample size was over twice Keenan’s, this was largely due to having contacted more authors, as response rate was only one fourth as large [26].

This study included the first authors of indexed journals. Though certainly a group with important knowledge related to malaria, this misses malaria control programme employees, health agency workers, and other

stakeholders. Their experiences and viewpoints may be different from those of academics, and arguably more relevant. The de-biasing method accounts for different response rates of “senior” vs. “junior” researchers, but does not take into account the fact that first authors are generally more junior than senior authors (i.e., the pool from which samples came may have been biased itself). To the extent that the results suggest that those with less experience (as represented through publications) tended to be more “optimistic” regarding eradication, it is reasonable to assume that the restriction of first authors may have led to an overly optimistic sample, making the results of the survey even more striking. Given these issues, the extent to which the respondents are representative of malaria experts cannot be known with certainty.

There are other important limitations which may also affect this study’s generalizability. The restriction of the source of data to only the PubMed platform meant not detecting researchers who publish in journals indexed elsewhere. Data was collected in late 2016 and early 2017, and the extent to which the opinions of participants have changed is unknown. Though the qualitative coding of free-text comments was reviewed by all authors, only one individual carried out the coding. This, along with the low response rate among invited participants, suggests that this study may have been subject to both selection and analysis bias; results should be understood within this context.

Conclusion

The findings of this survey show researchers expressing hesitance about the likelihood of eradication and suggesting a long-time frame until it is achieved. The causes for skepticism are diverse, but common themes were the need for innovation, systemic challenges, and the complexity of the disease and its transmission.

The implication of these results are twofold: (1) that those working or investing in eradication-specific campaigns, as well as those modeling these campaigns’ hypothetical cost–benefit, should factor in researchers’ perceived long time frame when calculating those campaigns’ expected value; (2) that champions of near-term eradication may need to make a more compelling case to malaria researchers of eradication’s feasibility, in order to better focus and inspire the latter.

The “true” feasibility and timeframe of eradication is unknown, as only time will tell whether the collective “wisdom” of researchers was worth adhering to or not. The actual cost–benefit of eradication interventions is not only a function of eradication’s success, but also of a number of other factors which are only knowable retrospectively. This study’s primary contribution is the provision of a snapshot of perceptions of malaria

researchers, whose opinions may be of value not only to other researchers, but also to the malaria and public health communities at large.

Abbreviations

GMEP: Global Malaria Eradication Programme; GMP: Global Malaria Programme; WHO: World Health Organization.

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Authors' contributions

JB conceptualized the study, coded the qualitative comments, carried out qualitative and quantitative analyses, and wrote the manuscript. MP contributed significantly to methods and quantitative analysis, and reviewed and edited the manuscript. JB contributed significantly to the qualitative methods and analysis, reviewed and edited the manuscript. QB contributed significantly to situating the manuscript in the appropriate research context, reviewed and edited, and contributed significantly to the literature and introduction. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was deemed IRB exempt since it did not involve any intervention on any human subjects, consisted only of researchers taking an online, voluntary survey. In the invitation to complete the survey, participants were provided with an info sheet: <https://docs.google.com/document/d/1zr7hW5Gys4qHIMBMT9AcfLCPAqqdIbzU-JjjMUXfEUQ/pub>.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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5. Study 2: Foreign direct investment, corporate social responsibility, and malaria control in Mozambique - trends, risks, and opportunities

Foreign direct investment, corporate social responsibility, and malaria control in Mozambique - trends, risks, and opportunities

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Abstract

Mozambique has a high ratio of foreign direct investment (FDI) to gross domestic product. Foreign firms' corporate social responsibility (CSR) activities often target malaria. Using publicly available datasets and a systematic review of both grey and academic literature, we quantify the magnitude of FDI and CSR activities over time in Mozambique, analyze the issues and trends associated with these activities, and discuss opportunities and risks for malaria elimination in the context of the private sector delivering a public good.

Introduction

Mozambique is a Southern-East African country with a surface area of nearly 800,000 m² (more than 3 times that of the United Kingdom) and a population of nearly 30 million inhabitants. Though low-income, Mozambique experienced an upward trend in gross domestic product (GDP) per capita from approximately 200 USD in the late 90s to 623 in 2014, followed by a steep decrease in 2015 down to 382 in 2016 (WB 2016).

Mozambique's economic growth up to 2014 was facilitated by the government's open policy towards foreign direct investment (FDI), a plentiful supply of natural resources (Rogers 2014), and relatively inexpensive labor. These factors combined to push Maputo (Mozambique's capital) into the top-20 African countries in terms of gross FDI (UNHabitat 2018). Its location (a large, eastward-facing coastline, proximity to rapidly developing South Africa, and integration into trade corridor and zones such as those with Zimbabwe

(UNHabitat 2018) and the Southern African community as a whole (Asiedu 2005)) are favorable to foreign investment, which is largely geared towards the export market, and heavily concentrated. 63% of exports come from aluminum, electricity, minerals, and gas, with each sector displaying high degrees of concentration (greater than 50% of the export share of the previous four industries are attributable to one company) (Sutton 2014). The total number of foreign enterprises operating in Mozambique is not ascertainable, but in both quantity and diversity of sources, FDI has increased dramatically in recent years (Sutton 2014). Mozambique was the Sub-Saharan African country with the greatest increase in FDI (defined by the World Bank as cross-border investment to establish a lasting interest) inflows from 2006 to 2014, registering a boom between 2010 and 2014 of about 5000 million USD (UNCTAD 2012).

The impact of FDI on economic growth and other economic indicators has been largely assessed (Alfaro et al. 2006) (Almfraji and Almsafir 2014) (Brundtland 1999). As FDI has been found to improve working conditions in low-income countries and, consequently, population ability to pay (Bloom and Canning 2008), they are likely to improve access to healthcare and, therefore, improve health (Feenstra and Hanson 1997). However, there is some evidence that FDI may have adverse effects on health, through increasing the consumption of “bads” such as tobacco and alcohol and the level of harmful pollution (Pazienza 2015) (Shahbaz et al. 2015). It has been recently assessed that FDIs are weakly associated with a marginal benefit in adults’ life expectancy in low and middle income countries (no impact has been found on children’s health), yet investments into the secondary sector (for being polluting) have been found potentially harmful (Burns et al. 2017).

In Mozambique, improvements in health have accompanied economic expansion, but the country still lags behind in many basic health outcomes (Williams et al. 2015). For example, clusters exist in Southern Mozambique with HIV prevalence as high as 40% (González et al. 2015).

Mozambique, like the majority of countries in Sub-Saharan Africa, is still characterised by a high burden of infectious diseases: one of them is malaria. Malaria is a protozoan parasitic disease, transmitted to humans by mosquitoes. The *Plasmodium falciparum* species, transmitted by the female *Anopheles* mosquito, accounts for a large majority of deaths (N. J. White et al. 2014). Estimates for the year 2015 quantify the burden of malaria in Mozambique in 8,300,000 cases and 15,000 associated deaths (WHO 2016). Despite the still high malaria burden, Mozambique is part of the “Elimination Eight (E8)” malaria initiative, with the country-specific goal of malaria elimination by 2030. Elimination efforts have been particularly active in Southern Mozambique, in border areas contiguous with Swaziland and South Africa, where the goal is elimination by 2020 (Moonasar et al. 2016).

Several economic activities are strictly linked to malaria. On the one hand, particularly agricultural-based and extraction activities are responsible for considerable increases in the malaria burden, through land and environment modifications that favor the efficiency of mosquitoes in spreading the malaria parasites (Sheela et al. 2017). On the other hand, the same activities, are barely carried out without consistent investment towards malaria management, both prevention and prompt treatment: firms need to protect their workers

against infections to maintain their productivity high. In this regard, there is little evidence on economic burden malaria places on the private sector in endemic countries: however, available reports point to profitability of funding malaria control (Nonvignon et al. 2016). Malaria control carried out by some multinational companies have been highly successful and strategies implemented were adopted as a model for the whole country (Asante et al. 2011).

Private investments in malaria control can be done as part of the “normal actions” of private sector or can go beyond what is strictly needed for having workers’ health to carry out activities and be seen as part of the corporate social responsibility (CSR). CSR is defined as those cases in which a company goes “beyond the legal requirements of the country in which they operate” in their work towards that country’s long-term interests, in such a systematic manner that it becomes “business as usual” (Ortega et al. 2016).

Motivations for engaging in CSR have been analyzed in the economic literature. Enterprises would have no incentives to engage in CSR according to Friedman (Friedman 1970) as firms are organized to maximize their profits only. The opposite view is that CSR is actually a strategy for maximizing profits. According to this vision, CSR helps enterprises to make their products known and, therefore, foment consumers’ demand (Porter and Kramer 2002). CSR also helps building a positive reputation of enterprises among institutions and communities where they operate: this is particularly useful for foreign firms that have no previous contacts with the host country/communities (Y. Zhu, Sun, and Leung 2013).

A US study showed that foreign firms are less likely to engage in CSR than domestic counterparts, but when they do engage, the magnitude is far greater (Blonigen and O’Fallon 2011). The reasons are not entirely clear: they could be cultural, or due to the scope of operations (foreign firms being more likely to participate in CSR at the “international” level).

The relationship between FDI and foreign aid may also be an interesting determinant of CSR: if aid from a particular country increases FDI from the same country to the same host communities, incentives to engage in CSR from foreign private companies may disappear (Selaya and Sunesen 2012). In other words, why should foreign companies donate to the host country when the government of the country of origin is already giving?

Private foreign investors showed a great optimism during the International Monetary Fund meeting held in Maputo, the Mozambican city capital, in 2014 (Pfeiffer et al. 2017). Beginning in late 2015, the flood of FDI into Mozambique (and many other subsaharan African nations) slowed to a trickle. The impact of this slowdown on CSR is not yet known, but it can reasonably be assumed that it will mean a reduction in CSR activities (albeit with lag). Almost in parallel to this, Mozambique has had serious financial problems which have resulted in default (Economist 2017). Given the rapidly changing economic and epidemiologic context in Mozambique, a comprehensive and current understanding of both (a) the landscape of FDI and CSR in Mozambique and (b) public health issues (namely, malaria control) which are directly affected those investments is sorely needed. Such an understanding may foster greater private interest in for-profit investment in public health measures. Likewise, it can facilitate better public sector understanding of potential

industry partners and stakeholders (a prerequisite to greater public-private collaborations), and guide the public sector away from an inflexible dependence on FDI for the provision of public health necessities.

We carried out a systematic review of economic and public health research pertaining to FDI, CSR, malaria and Mozambique. This paper gives an overview of trends in FDI and CSR in Mozambique as well as a synthesis of academic literature on the topic, with a focus on its impact on malaria control. It is by no means comprehensive, but offers a consolidated starting point for understanding both the place of FDI and CSR in the literature, as well as where the interests and incentives of the public and private sectors converge and differ in regards to malaria control.

Methods

We sought to identify and describe sources of information regarding FDI and CSR in Mozambique, particularly in regards to malaria control and elimination. We carried out this identification process via 2 distinct approaches to understanding FDI, CSR and malaria in Mozambique:

1. Identification and analysis of quantitative datasets.
2. Systematic review of both grey literature (news, company websites, etc.) and academic literature.

Quantitative datasets

We examined trends from multiple datasets related to FDI, CSR and malaria in Mozambique. These included the “Doing Business” data pertaining to the measurement of regulatory efficiency (WB 2016), the GADM (Gadm 2009), the Deutsche Bundesbank Data Repository for foreign exchange rate history (Bundesbank 2015), the Knoema World Data Atlas for macroeconomic trends (Knoema 2015), the World Bank data portal for information containing to net foreign inflows and FDI, USAID Demographic and Health Survey data on sociodemographics and health-related practices (WB 2017), the Instituto Nacional de Estatística for granular data pertaining to Mozambique’s population and economic activities (INE 2017), the Institute for Health Metrics and Evaluation data pertaining to disease trends over time (IHME 2015), the International Monetary Fund’s open datasets pertaining to FDI (IMF 2003), and the United Nations Conference on Trade and Development’s data on FDI (UNCTAD 2012).

Systematic review

Grey literature

Our grey literature review followed known practices (Godin et al. 2015, Adams et al. (2016)), relying on internet searches and linked references. Sources include, but are not limited to UN reports on economic trends, WHO reports and brochures pertaining to health trends, company websites and brochures, newspaper articles, and think-tank white papers.

We devised 2 simple search queries, and use www.google.com and www.bing.com to retrieve results. The queries were:

1. Mozambique foreign direct investment malaria
2. Mozambique corporate social responsibility malaria

Academic literature

In order to gauge research attention and focus on FDI and CSR insofar as they affect Mozambique and malaria, four systematic searches were carried out using the EBSCOhost and NCBI/pubmed databases. Our search queries are detailed below:

1. "(malaria) and (corporate social responsibility)" (no results found in EBSCO)
2. "(malaria) and (foreign direct investment)"
3. "(mozambique) and (corporate social responsibility)" (no results found in EBSCO)
4. "(mozambique) and (foreign direct investment)"

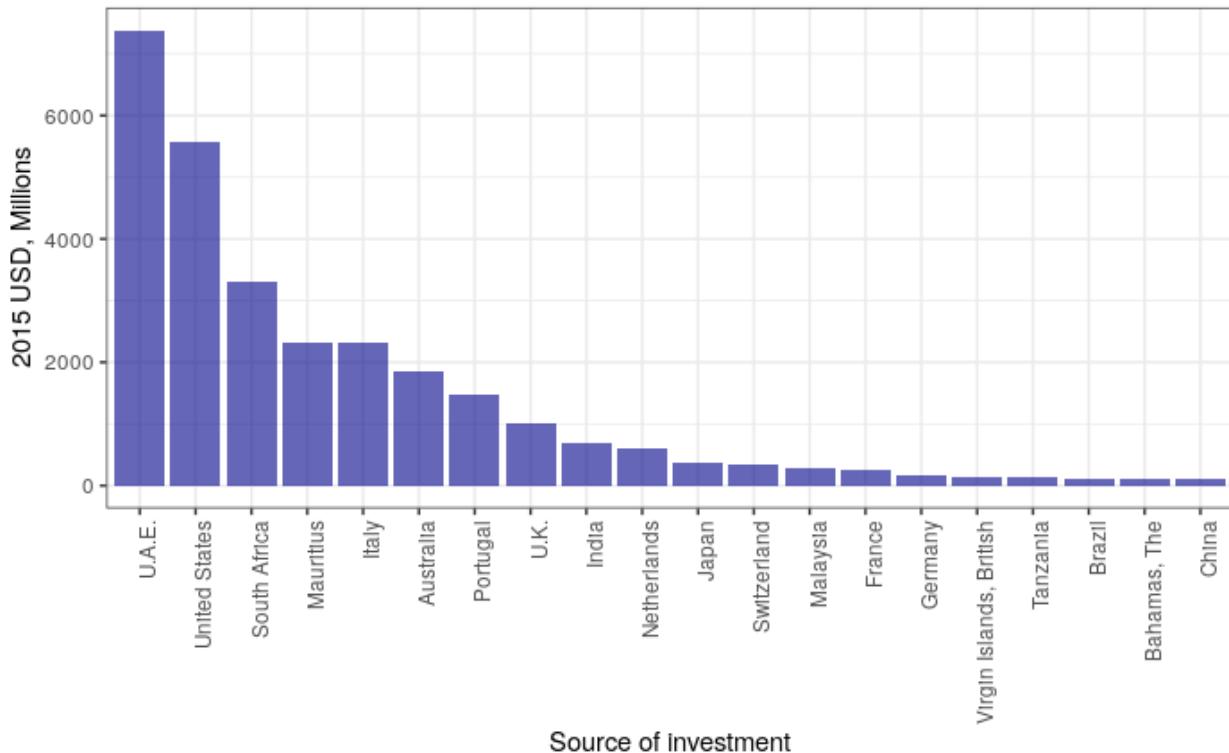
Results

Quantitative datasets pertaining to FDI and CSR in Mozambique

According to the IMF, 69 countries had foreign direct investment in Mozambique as of the end of 2015. The below chart shows the top 20 countries ranked by amount invested in Mozambique.

Sources of FDI In Mozambique

By investor country



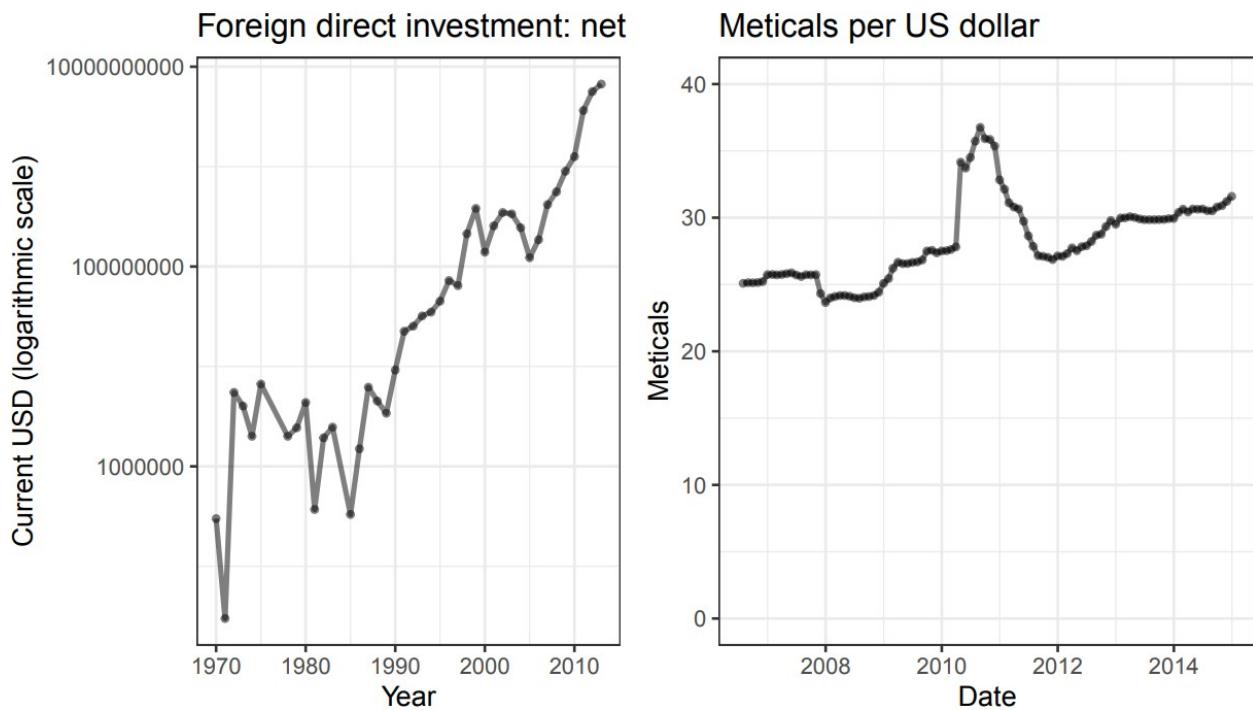
Though reliable data only go as far back as 2009, the landscape of investment 20 years prior would have been both (a) far smaller and (b) primarily composed of western countries, especially given that Mozambique emerged so late from civil war (1994). As of 2014, Chinese capital had entered into 52 countries in Africa (UNHabitat 2018), and though more recent data are not available, it's likely that this figure has grown since then. Though as of 2015, China did not figure in the top 20 FDI countries in Mozambique, its upward trend is notable, with approximately 1.5 million USD invested in 2010 to nearly 100 million by 2015 (a 60-fold increase). As of 2017, 3.2% of Chinese FDI flows went to Mozambique (He, Xie, and Zhu 2015). Though much of the growth is fueled by centralized State actors, an increasing number of provincial and decentralized investors are playing a role in African FDI (Gu et al. 2016).

Massive increase in FDI

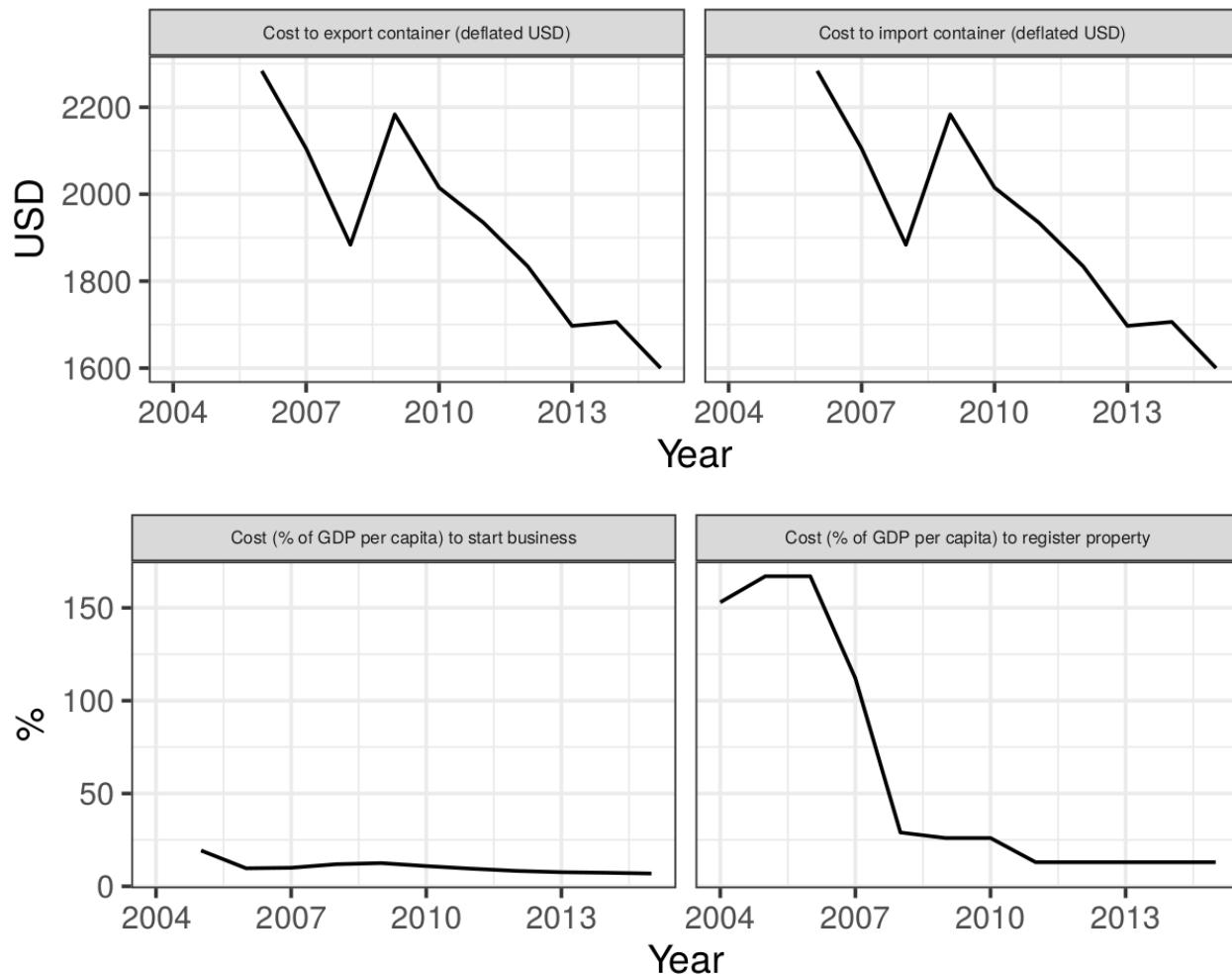
Following independence (1974), Mozambique saw two decades of low and unsteady foreign investment, largely due to the civil war (which did not end until 1992). Thereafter, foreign investment began a steady increase but leveled off by the late 1990s. However, the discovery of novel sources of oil and gas set off a new spur of investments beginning in 2007, and continuing through last year. From 2010 to 2013, foreign direct investment grew from 1.26 to 6.70 billion USD, a more than five-fold increase (WB 2015).

In addition to the discovery of new resources, recent growth has also been fueled by political and economic reforms which have made it easier for foreigners to do business in

Mozambique. Of particular note, inflation remained relatively low (at least through 2014) (Bundesbank 2015).



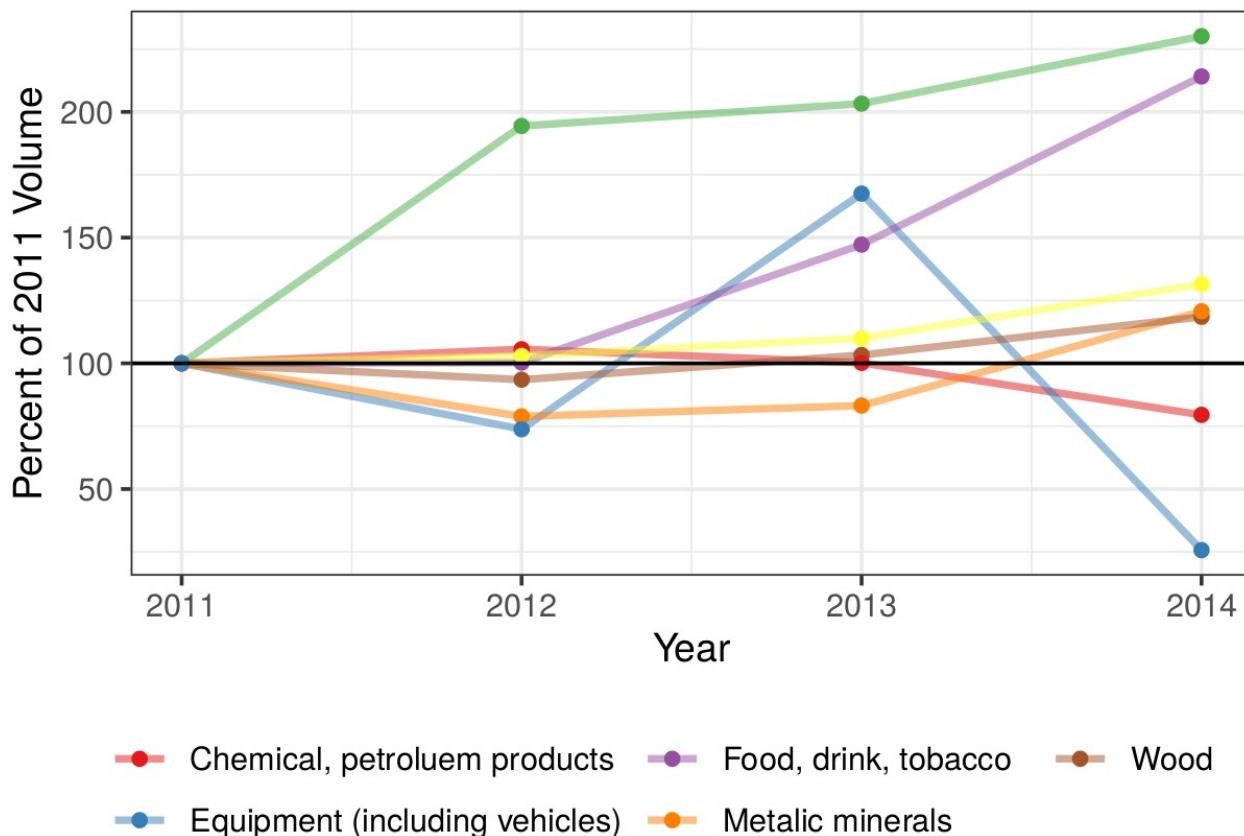
The massive increases in FDI have also been facilitated by dramatic decreases in the costs to import and export, as well as the costs of starting a business and registering property (WB 2016).



Breakdown by industry

Most of recent growth has come in the “extractive” industries, a term encompassing a range of industry, but in the Mozambican context largely applying to hydrocarbons and mining (INE 2015).

Industry volume index

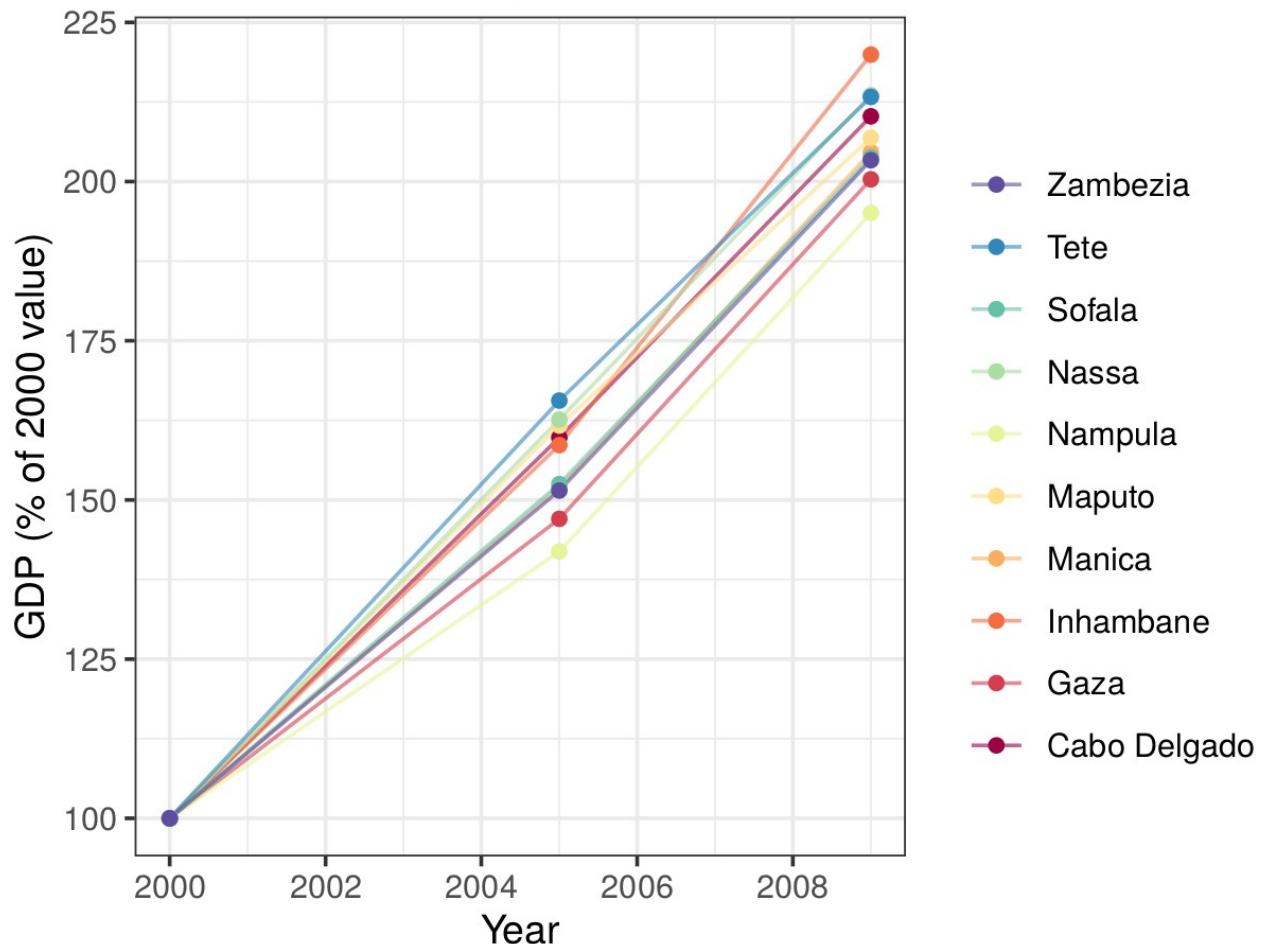


The late 2015 economic slow-down in the developing world, particularly the low price of oil, could have serious repercussions for FDI in Mozambique. That said, the mining of metals and the service industries both make up a larger share of Mozambique's economic output than the extraction of hydrocarbons, which should somewhat buffer the Mozambican economy from the negative effects of low oil prices.

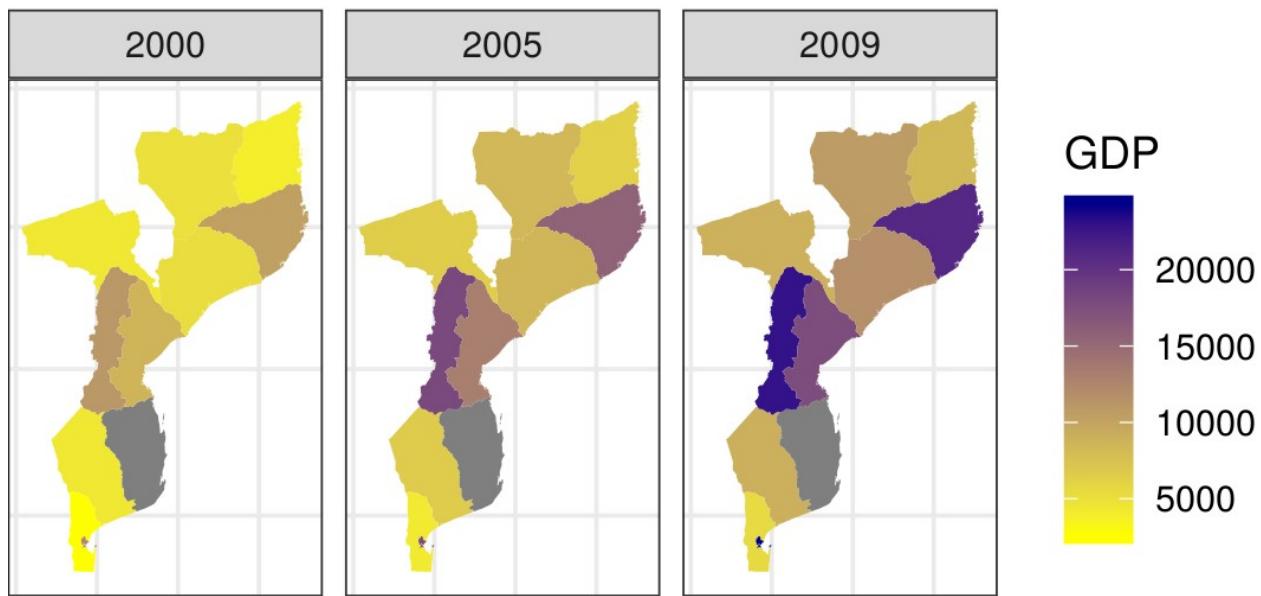
Breakdown by region

Despite the concentration of private investment in regional projects, growth has been similarly large in all provinces. From 2000 to 2009, GDP approximately doubled, with the greatest growth occurring in Inhambane (119% growth from 2000 to 2009), and the least robust growth in Nampula (95%) (Knoema 2015).

Province-specific growth in GDP



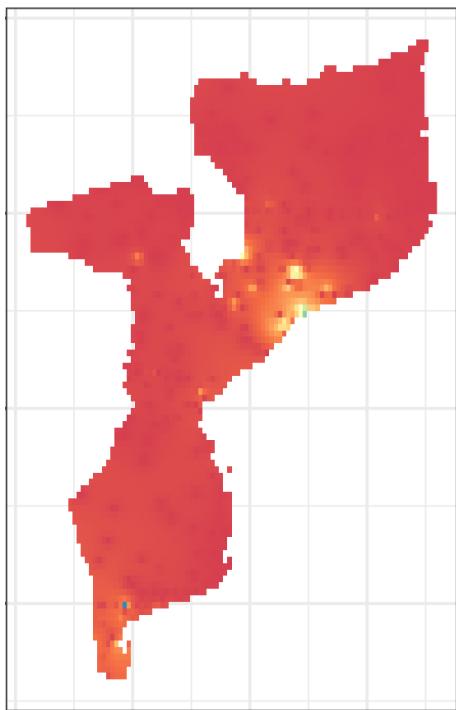
The homogeneity in growth comes somewhat as a surprise, as it defies the general developing world pattern in that growth in areas that already had high GDP (Maputo and the coastal provinces) was as robust as growth in areas with previously low GDP.



FDI is associated with CSR. Whether under the guise of CSR or not, it is noteworthy that the private sector currently does play a role in malaria control activities. According to 2011 DHS data, greater than 7 in every 1,000 households had a private company carry out indoor residual spraying (DHS 2011). And, in some clusters, the percent of houses covered by private IRS was greater than 25%.

Interestingly, though the UN data indicated that corporations don't actively engage in malaria control as part of CSR, the geographic distribution of households which had their homes sprayed by a private entity are clustered in areas where foreign firms operate, particularly in the south (around Maputo) in the East, where extractive industry activity is highest.

Privately supplied IRS



Systematic review

Grey literature

Grey literature search results

Google returned 266,000 results for the former query, and 240,000 for the latter (506,000 in total); Bing returned 4,620 and 20,900, respectively. We screened the top 50 results from both services (a total of 100 items) for both queries. For the former, of the 100 items identified, 33 were identical in both search engines (yielding a total of 67 unique items); in the latter, 39 were identical (yielding a total of 61 unique items).

Grey literature synthesis

Our grey literature review returned relatively little information which was not readily available in those sources uncovered in the data review and systematic review. Very few foreign companies operating in Mozambique have any publicly available information regarding corporate social responsibility activities.

Corporate social responsibility in Mozambique is new in nomenclature, but activities which could be classified as CSR have existed for decades. The number of firms actively engaging in CSR cannot be ascertained (given the large and ever-changing number of small businesses), but virtually all of the largest firms, both foreign and domestic, have a CSR component.

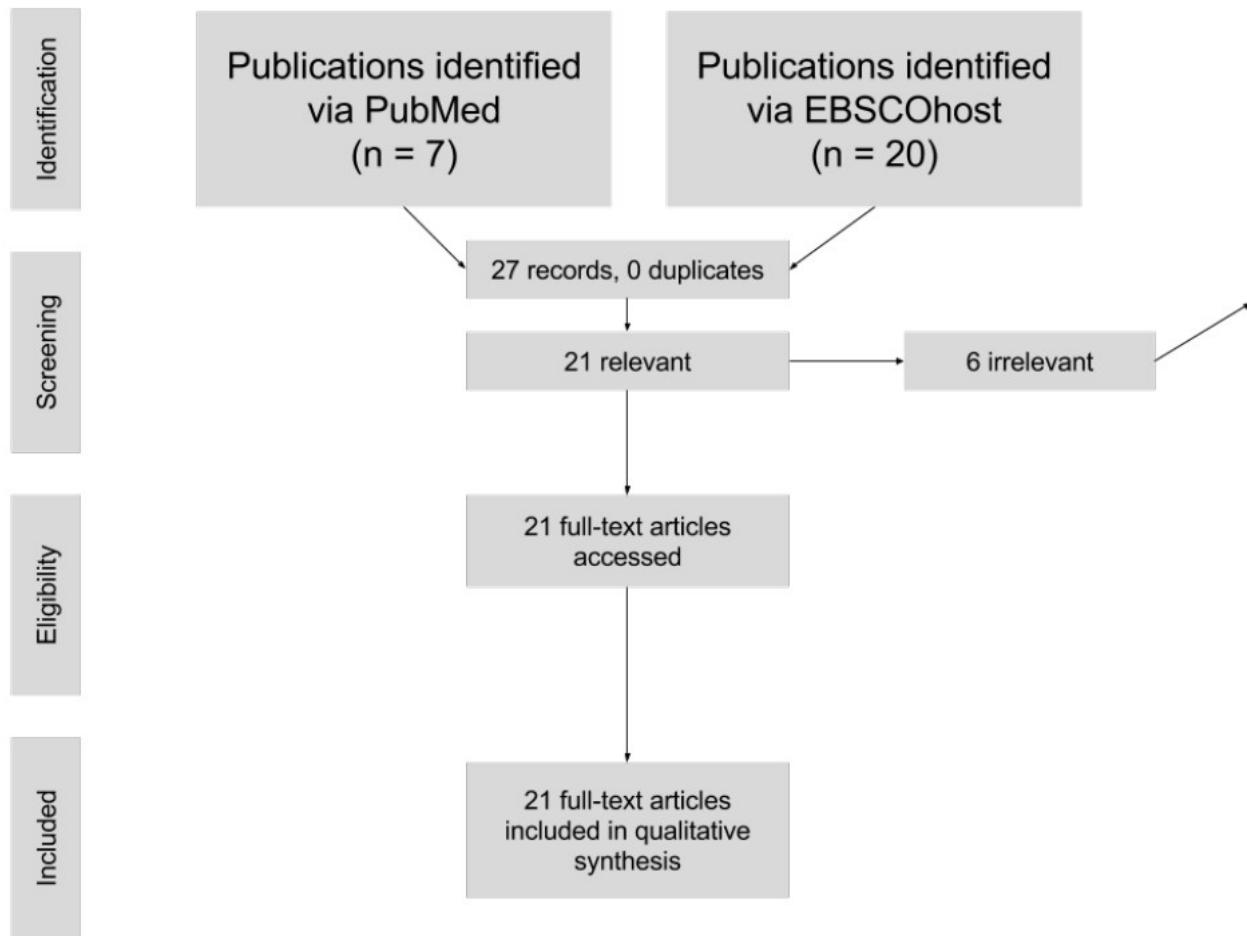
Firms with CSR activities are often large and foreign. Among the largest “key players” in Mozambican CSR are Coca-Cola, British Petroleum and Colgate-Palmolive. State conglomerates, such as Águas de Moçambique and Electricidade de Moçambique, also participate in CSR activities (Compact 2007). Large communications firms, such as Vodacom and MCEL, and banks (BIM and BCI) have a CSR component, but generally focus on culture, environment and sport, avoiding activities which could either complement or conflict with the health sector. Much of CSR in Mozambique is basic services only, a phenomenon Kaufmann described as “CSR towards compliance” as opposed to “beyond compliance” (Kaufmann and Simons-Kaufmann 2015).

Among major foreign companies, those operating in extraction - particularly mining - appear to be the most involved with malaria. BHP Billiton has been active in vector control support to the governments of Mozambique, Swaziland, and South Africa, particularly in the early 2000s (BHP 2014). Kropfmühl AG and Vale, also mining companies, have carried out CSR related to both community development and malaria control in Northern Mozambique (Kaufmann and Simons-Kaufmann 2015).

Most CSR-funded activities are focused on education, community development, women’s rights and entrepreneurship. According to a UN poll, none of the country’s largest firms invest directly in malaria-related CSR activities (Compact 2007). That said, a majority of the firms interviewed by the UN indicated that one of the principal reasons for investment in CSR is to complement government efforts. To the extent that malaria accounts for more of the loss in disability-adjusted life years in Mozambique than comparable countries (IHME 2015), malaria control’s lack of representation among core CSR activities is a notable absence. One important exception is the Nando’s-lead Goodbye Malaria Trust, an umbrella organization which includes a development impact bond, the Goodbye Malaria initiative, and partnerships with several other foreign firms operating in Mozambique.

Academic literature

Our search is outlined in the below PRISMA-based diagram.



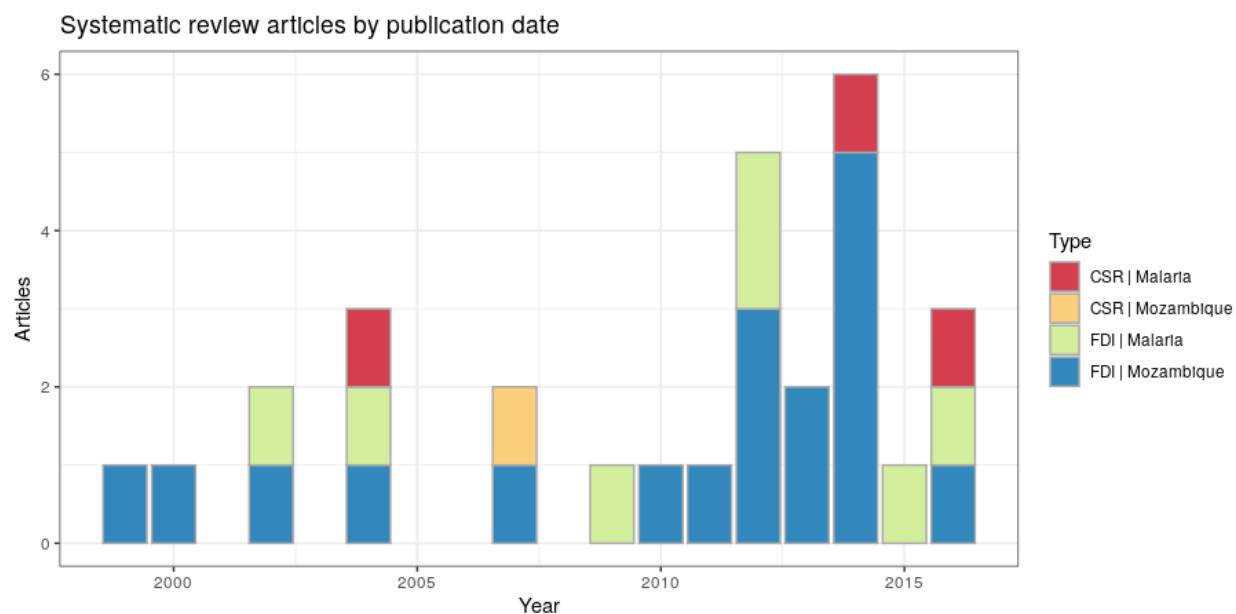
The 6 papers flagged as “irrelevant” were classified as such when the abstract revealed that the terms in question were not directly related with the paper. The below table shows the results retrieved for the systematic review. Full article information is in the bibliography

Source	Year	Title	Type	Author
EBSCOhost	2009	Public Governance, H...	FDI Malaria	Azemar, et al
EBSCOhost	2014	A Critical Review of...	FDI Mozambique	Mahembe, et al
EBSCOhost	2000	Administrative barri...	FDI Mozambique	Emery, et al
EBSCOhost	2012	Attracting Foreign D...	FDI Mozambique	Tembe, et al
EBSCOhost	2013	Contemporary Process...	FDI Mozambique	German, et al
EBSCOhost	2012	Corruption and Multi...	FDI Mozambique	Grande, et al

EBSCOhost	2014	Determining the Natu...	FDI Mozambique	Winkler, et al
EBSCOhost	1999	Foreign Direct Inves...	FDI Mozambique	Morisset, et al
EBSCOhost	2014	Growth, Capital Accu...	FDI Mozambique	Castel-Branco, et al
EBSCOhost	2007	Linkage Between fore...	FDI Mozambique	Wilson, et al
EBSCOhost	2012	Mining FDI and Infra...	FDI Mozambique	Robbins, et al
EBSCOhost	2013	Potential and actual...	FDI Mozambique	Winkler, et al
EBSCOhost	2004	Regional integration...	FDI Mozambique	Goldstein, et al
EBSCOhost	2014	Sector Case Study: M...	FDI Mozambique	Barnard, et al
EBSCOhost	2011	Strategic Privatisat...	FDI Mozambique	Buur, et al
EBSCOhost	2016	The Economics and Po...	FDI Mozambique	Hansen, et al
EBSCOhost	2002	The Role of FDI in E...	FDI Mozambique	Bjorvatn, et al
EBSCOhost	2010	Uncovering Trends in...	FDI Mozambique	Warren-Rodriguez, et al
EBSCOhost	2014	Sector Case Study: A...	FDI Mozambique	Barnard, et al
Pubmed	2004	Community health out...	CSR Malaria	Singer, et al
Pubmed	2014	Public-private partn...	CSR Malaria	Hutton, et al
Pubmed	2016	Examples of coupled ...	CSR Malaria	Singer, et al
Pubmed	2007	Feasibility of water...	CSR Mozambique	Tang, et al
Pubmed	2002	The economic impact ...	FDI Malaria	Mills, et al
Pubmed	2004	The economic burden ...	FDI Malaria	Russell, et al

Pubmed	2012	The economic benefit...	FDI Malaria	Feachem, et al
Pubmed	2012	Global health fundin...	FDI Malaria	D'Agostino, et al
Pubmed	2015	Tracking Global Fund...	FDI Malaria	Huntington, et al
Pubmed	2016	Investing for Impact...	FDI Malaria	Zorzi, et al

The below chart shows our systematically retried publications by date. What is most striking is how little academic attention has been given to CSR, with none given to the intersection of CSR and malaria.



Qualitative synthesis of systematic review of academic literature

The literature is largely clear on two points: (1) that economic growth in Mozambique has been fueled in large part by foreign direct investment, and (2) that economic growth has been accompanied by a rapid decrease in malaria morbidity and mortality. There is no clear consensus regarding the extent to which the former is a result of the latter, and researchers disagree on how much of a role FDI has played in improving the social and economic conditions of Mozambicans.

Mozambique has a unique social and economic system, which is particularly attractive to foreign investment. The Mozambican economy is “oriented to incentivize large-scale FDI

projects” (Robbins and Perkins 2012). Land distribution, for example, despite being *igualitarian de jure* has been *de facto* aimed at satisfying the interests of large foreign firms (German, Schoneveld, and Mwangi 2013). In extractive industries, and particular the sugar industry, the state has gone so far as to encourage unprofitable enterprise by propping up an internal market so as to keep foreign inflows of cash from drying out, a process described as a “mediating bureaucracy” (Buur, Tembe, and Baloi 2012). Another part of the attraction of FDI to Mozambique is the extent to which the state and society, both formally and informally, subsidize the cost of labor by allowing for below subsistence wages.

In one view, the last two decades of economic growth are largely irrelevant to the well-being of Mozambicans due to the “porous and extractive” nature of FDI (Castel-Branco 2014). In other words, since both investment and profit are largely external to the Mozambican economy and society, “positive spillovers” into local firms are few and far between (Winkler 2013).

CSR is one way of offsetting the trend, and its potential for mutually beneficial effects is high, particularly when its resources target malaria control. Per one analysis, malaria elimination in an endemic country like Mozambique would lead to a 16% increase in FDI (Azemar and Desbordes 2009). The possibility of re-directing resource rents to socially beneficial ends is acknowledged by multiple authors (Robbins and Perkins 2012, Castel-Branco (2014)).

However, the redirection or resource rents to CSR is complicated. If coerced (through higher taxes or fewer incentives to investment), the recent decrease in FDI may be exacerbated. If voluntary, particularly in the case of expenditures in medicine and health, the public’s health would be largely dependent on private whim, a recipe for unsustainability at best and potential epidemiologic catastrophe at worst.

In summary, Mozambique’s high ratio of FDI to GDP and general allowance of “porous” foreign investment represents an opportunity for scaling up the private sector’s engagement with public health, as a means to offset the lack of social benefits that traditional FDI has entailed. A coercive (tax-based) approach to scaling up this engagement may lead to a withdrawal of FDI from the country. The alternative, an increase in CSR, is a possible route for creating synergies, particularly in the case of malaria elimination.

Discussion

The intensity of CSR activity seems to closely track FDI, but generally avoids malaria control. The few malaria-related CSR projects in recent years has come in large, “mega-projects” whose well-publicized malaria abatement activities are profit-driven (Mouzin and al. 2011) or whose primary aim is not profit-related (Han 2015). This should come as no surprise given that “mega-projects” make up a majority of FDI to Mozambique (albeit declining slightly in recent years) (UNCTAD 2012). Though the former is often portrayed as a “win-win” for business and public health, the latter also offers tangible benefits for private industry, and should be understood as operating under the same conditions and with the same motivations. To the extent that most CSR activity has avoided the health

sector (including malaria) in favor of cultural, environmental, education and more general “development” activities, it is reasonable to assume that this may be due to the perceived costs of malaria control, lack of perceived PR benefits, the government and NGO’s predominant role in the area, as well as the “opt-in” nature and privacy/legal issues generally related to engaging in health-related campaigns.

Scaling up malaria control through CSR: opportunity and risk

Opportunity

The historical absence of malaria-related CSR represents an opportunity for complementarity. In addition to improvements in public health, both the private and public sectors stand to benefit economically from a scaling up of malaria control driven by the private sector. By increasing malaria control activities, as a share of total CSR expenditures, public funds could be redirected towards other areas of health. Likewise, if private CSR activities pivoted towards malaria control rather more general philanthropic gestures, CSR would have a more direct impact on wellbeing (with less temporal lag), thereby fulfilling the public relations goals of the firms that invest in CSR. Finally, for many industries, the firm itself is a potential direct beneficiary, given that improvements in employee health and a reduction in employee absenteeism can be directly correlated to productivity.

Risk

Scaling up CSR while also encouraging its redirection towards malaria control is not without risks. The most notable downfall of this approach is the potential for the inadvertent dependence on the private sector for what is essentially a public good. Were CSR targeting malaria control to reach significant levels (and the government were to enact a corresponding redirection of funds towards the financing of other health areas), then a situation would be created in which the public sector had essentially divested from a public good. This would be unwise and dangerous.

A secondary risk is that increased private sector involvement in malaria control could cause a decrease in public sector *competence* in the prevention and treatment of malaria. This could have negative consequences in the case of either a financial or economic crisis (in which CSR activity would be curtailed) or an increase in malarial activity. By the same token, CSR involvement in malaria control could potentially portend, at least initially, less effective interventions. Private firms’ incentives, though aligned with the public’s in terms of malaria, are not identical, and pressures from shareholders and for positive public perception might motivate malaria control strategies which do not necessarily carry with them the most recent scientific knowledge. The methods by which private initiatives could contribute to malaria elimination and control while at the same time only “complementing” (rather than “substituting”) State activities is not entirely clear, and would require significant organization (Kaufmann and Simons-Kaufmann 2015).

A third risk is a lack of coordination. Both in terms of logistical activities as well as biological realities (drug and insecticide resistance, etc.), coordination of malaria control activities is absolutely essential if Mozambique is going to make the transition to

eradication. The issue of coordination could be solved through an activities and outcomes reporting/surveillance structure (necessarily managed by the state), but compliance could be problematic.

A final risk is that of volatility. By centralizing malaria control under the auspices of the government, public health authorities can effectively distribute malaria control expenditures to where and when they are most needed. If this control were only in the hands of private firms, expenditure would likely transform into a function of firm-specific profitability and shareholder incentives, as well as market cycles. This could lead to a situation in which malaria control activities are most prevalent in areas where the economy is strongest, rather than areas where the need is greatest, with inequity implications.

Conclusion

High FDI in Mozambique and growing interest in CSR both call for increased reflection on the private sector's role in the delivery of public goods. A refocusing of CSR expenditures into areas where the need is greatest (specifically, malaria control) could lead to better health and greater profits, and go beyond the perception of superficial CSR which doesn't address core social problems (ie, "green washing") (Kaufmann and Simons-Kaufmann 2015). This "win-win" for the public and private sectors represents a rare opportunity, which deserves more discourse, research and experimentation.

That said, the growing interest in CSR suggests both that (a) the need for services exist and (b) that corporations (especially foreign firms) have enough excess capital to finance these services. Both of these factors suggest the need for a better-fitting taxation rate, and a more efficient delivery of public services. That said, in the short-term, increasing the efficiency and effectiveness of CSR activity through a re-pivoting towards malaria control should remain a goal.

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6. Study 3: Evidence of high bednet usage from a list randomization in rural Gambia

RESEARCH

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Evidence of high bed net usage from a list randomization experiment in rural Gambia

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Abstract

Background: Recording behaviours that have the potential to impact health can be doubly challenging if the behaviour takes place in private spaces that cannot be observed directly, and where respondents answer what they think the recorder may want to hear. Sleeping under a long-lasting insecticidal net (LLIN) is an important intervention for malaria prevention, yet it is difficult to gauge the extent to which coverage (how many nets are in the community) differs from usage (how many people actually sleep under a net). List randomization, a novel method which partially obscures respondents' answers to sensitive questions, was employed to estimate LLIN usage in The Gambia.

Methods: 802 heads-of-household from 15 villages were recruited into a randomized controlled trial assessing the effect of a housing intervention on malaria. These houses were randomly assigned to a housing intervention versus control, with stratification by village so as to ensure balance between arms. From these, 125 households (63 intervention, 52 control) were randomly selected for participation in the list randomization experiment, along with 68 households from the same villages but which were not part of the housing improvement study, resulting in a total of 196 households for the list randomization experiment. Approximately half ($n=97$) of the 196 study participants were randomly assigned to the control group and received a four-question list about non-sensitive behaviours; the intervention group ($n=99$) received the same list, with the addition of one question on a sensitive behaviour: whether or not they had used a bed net the previous night. Participants were read the list of questions and then said how many of the statements were true. Bed net usage was estimated by calculating the difference in means between the number of affirmative responses between the two groups.

Results: The mean number of affirmative responses in the control group was 2.60 of four statements (95% confidence interval, 95% CI 2.50–2.70), compared with 3.68 (95% CI 3.59–3.78) in the intervention group. Such difference (1.08; 95% CI 94.9–100%) suggests near universal bed net usage.

Conclusions: Bed net usage by household heads in these rural villages was found to be high. Though not entirely unexpected given other studies' estimates of high bed net usage in the area, the list randomization method should be further validated in an area with lower coverage.

Keywords: Malaria, List randomization, Long-lasting insecticidal nets, Gambia

Background

From 2000 to 2015, the burden of malaria was reduced substantially in sub-Saharan Africa (SSA), with the prevalence of falciparum malaria declining by half and an estimated 663 million cases averted [1, 2]. This extraordinary achievement is due to the massive deployment of long-lasting insecticidal nets (LLINs), indoor residual

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spraying and prompt, effective treatment. Despite these gains, progress has stalled recently, with malaria cases rising slightly from 210 million in 2010 to 219 million in 2017 [2].

Scale up of LLINs and prompt and effective case management [3] were factors in averting 68% of cases [1]. LLINs protect users by providing a physical barrier to night-time biting mosquitoes and by killing mosquitoes upon contact. At around \$7 per net distributed, they are a highly cost-effective intervention [3]. LLIN coverage in SSA has never been higher, with 80% of households having at least one net in 2016, and 43% of households having one or more nets for every two people [2]. However, there are concerns about how ‘coverage’ is measured and the extent to which high LLIN coverage translates to high usage [4].

Coverage is defined as the proportion of households with at least one LLIN for every two occupants [5], a metric that can be verified by counting the number of nets compared to the number of sleeping places. However, assessing bed net use, i.e., whether an individual actually sleeps under a net, is more difficult than assessing coverage. For example, while a household’s number of LLINs might surpass the threshold defined for coverage, household residents’ actual use may diminish after mass distribution campaigns due to product “wear and tear” [6], changes in use by season, social events, raised ambient temperature, and other factors. Assessments of LLIN usage often occur immediately after they are distributed, which may overestimate usage rates that are likely to decline over time. For example, a recent multi-country study suggested a 50% reduction in usage in the 23 months following LLIN distribution [7]. Perhaps of greater concern is the difficulty of estimating LLIN usage without directly observing people sleeping; studies usually rely on questionnaires and/or observing net(s) in a house. A recent meta-analysis estimated that self-reported rates of LLIN use were 13.6% greater than directly observed rates [8]. The extent of the gap between observed and reported usage is highly variable by country and social group [9].

The existence of this gap suggests that LLIN usage is potentially a sensitive behaviour. Reporting sleeping under a net is likely to be biased, since most recipients have been told that the net is protective. As a matter of politeness, or perhaps even fear of negative repercussions, respondents may say they have used the net, even when they have not. One method to reduce social desirability bias is list randomization [10, 11]. In a list randomization experiment, participants are divided into “control” and “treatment” groups. The control group is given a series of yes/no questions about everyday activities (communication, transportation, eating, and work),

but instead of answering each question individually, participants simply tally the number of “yes” responses and report that number to the researcher. The experimental group is provided with the same questions, but with an additional question on a sensitive behaviour. Using list randomization, participants from both groups are able to obscure their item-specific responses from the researcher, but the data generated from the process allows for aggregate comparison between the groups, with the difference in total “yes” items approximating the population-level “yes” prevalence of the item in question.

List randomization has previously been used to reduce data bias pertaining to sensitive topics, such as personal finance [12], intimate partner violence [13], illegal migration [14], and attitudes regarding homosexuality and gender [15]. Many studies find higher rates of socially-sensitive behaviours via list randomization than direct questioning, suggesting that list randomization could be an effective tool for eliciting unbiased responses pertaining to socially-sensitive behaviours [16]. However, when Haber and colleagues compared list randomization responses to assess HIV status and sexual behaviour with known individual-level statuses, the former performed poorly [17]. In other words, though list randomization may be a useful method for gauging behaviours subject to social desirability bias, other biases may come into play. Despite its relevance to public health campaigns and its sensitive nature, there are no published reports on list randomization applied to the question of LLIN use. Thus, the present study employed list randomization to estimate LLIN use in an area of seasonal malaria transmission.

Methods

Study location

The study was carried out in the Upper River Region (URR) of The Gambia (13.12 N, 14.1 W). The URR is an area of open Sudanese savannah divided into north and south banks by the River Gambia. The climate consists of a long dry season from January to June, with rainfall occurring between June–July and October. Most clinical malaria cases are observed in October–December [18]. The Gambia has a long tradition of bed net use, particularly in rural areas [19].

Study design

The list randomization experiment was part of a larger study on housing improvement and malaria. 91 villages were enrolled in a two-armed, household-clustered, randomized controlled trial using a block design (with the village as the block and households as the randomization unit) to assess the impact of housing improvement on malaria outcomes. Further details on the randomization

and clustering design are available in the study protocol [20].

Fifteen of the 91 trial villages were randomly selected for an ancillary longitudinal socio-economic study, stratified by riverbank (north vs south), ethnic group (with the purposely selection of one, Jagajari, for being the only Serrehule village in the trial), and size. The list randomization experiment was included in one of the four rounds composing the socio-economic study. 196 households were selected for participation in the list randomization experiment. The selection included both thatched-roof and metal-roof houses. The list randomization component took place from the end of November 2017 (approximately peak transmission) to mid-January 2018 (when mosquito density was low). A total of 1513 LLIN were distributed by the *RooPfs* trial in 2015/2016 before the trial started and a national campaign carried out by the National Malaria Control Programme (NMCP) also distributed free LLINs in July 2017, a few months before the list randomization experiment.

Enrolled household heads were randomly assigned using a simple randomization script in Visual Basic to one of two “question lists”: 97 received the control questionnaire and 99 the experiment questionnaire. The control questionnaire contained four questions about daily activities; the experiment questionnaire contained the same questions, with an additional question asking whether the participant slept under a LLIN the previous night (Table 1). The order of statements in all questionnaires was randomized at the individual level, thus, every household head had his or her own randomly assigned questionnaire. The maximum number of statement combinations [$N^*(N - 1)$] was 12 (4^*3) in the control group and 20 (5^*4) in the experimental group. Therefore, 12 and 20 different typologies of questionnaires were randomized to the households.

A trained field assistant obtained written, informed consent from the identified household heads, and administered the question list to them using their preferred local language in their household compound. Participants were asked not to address individual statements, but

instead to count on their fingers (held behind their backs, so as to block the view of the interviewer) the number of statements which were true for them. The reported number of true statements (0 to 4 for the control group, 0 to 5 for the experimental group) was recorded.

The sample size of 196 participants, chosen based on operational limits (budget and field assistant availability), was sufficient for the calculation of a 95% confidence interval with a margin of error of 5% on a LLIN usage point estimate of 85%.

Ethics

Participants were enrolled into the study provided they gave their full and informed written consent. The study was approved by the Gambia Government and Medical Research Council's joint ethics committee.

Results

196 household heads freely agreed and completed written informed consent to participate in the list randomization experiment. Comparison of important variables were similar in both experimental groups (Table 2).

Unbiased bed net coverage estimates via difference in means

The mean number of agreements in the control group was 2.60 (95% confidence intervals CI 2.50–2.70) of four questions. In the experiment group, the mean number of agreements was 3.68 (95% CI 3.59 to 3.78) of five questions. The difference of 1.1 is indicative of 100% bed net usage among the study population. A 95% confidence interval of the difference was estimated via t-test to be 94.9–100% ($t=15.67$, $p<0.001$). Notably, no respondents reported the minimum (zero) or maximum (four or five, depending on the group) number of activities from the list.

Discussion

Though the individual bed net status of participants is unknown to the field assistant and researcher, aggregating by group allows one to estimate the percentage

Table 1 List randomization question list

Control	Experiment
I used a telephone yesterday	I used a telephone yesterday
I used transportation other than walking yesterday	I used transportation other than walking yesterday
I ate benachin yesterday	I ate benachin yesterday
I worked yesterday	I worked yesterday
	I slept under a mosquito net last night

The statement in bold represents the “experimental” item. “Benachin”, also known as “jollof rice”, is a staple meal in the Gambia

Table 2 Characteristics of study groups

Variable	Category	List randomization group	
		Control	Treatment
Housing improvement intervention	Intervention	30 (30.9%)	33 (33.3%)
	Control	34 (35.1%)	28 (28.3%)
	Not in study	33 (34.0%)	35 (35.4%)
Ethnicity	Fula	60 (61.9%)	61 (61.6%)
	Mandinka	33 (34.0%)	33 (33.3%)
	Sarahule	4 (4.1%)	4 (4.0%)
	Unknown	0	1 (1.0%)
Village size	Large	33 (34.0%)	33 (33.3%)
	Small	64 (66.0%)	66 (66.7%)
River bank	North	31 (32.0%)	33 (33.3%)
	South	66 (68.0%)	66 (66.7%)
Gender	Male	52	50
	Female	45	45
	No response/missing	0	4
Age	Mean	44.7	44.6
	Standard deviation	8.12	8.25

of participants who agreed with the experimental statement, since in all other aspects the participants' responses should converge towards being identical due to random assignment. As with other list randomization experiments, it was assumed that (i) the introduction of the experimental item would not affect responses to other items and (ii) that the degree of accuracy to non-experimental items would be similar across groups (i.e., the "no design effect assumption" [21]). Accordingly, the difference between the average number of agreements in the two groups, with uncertainty quantified by a t-test, should reflect the proportion of participants in the experiment group which agreed with the experimental statement.

The experiment indicates very high bed net use by household heads in rural eastern Gambia (94.9–100%). The estimate of virtually universal LLIN usage is significantly higher than previous published figures on LLIN coverage obtained via other methods [18]. For example, net coverage in 2010 in the Upper River Region, including the urban areas, was only 68% [22], and a 2017 national survey showed that 75.7% of the Upper River Region population had de facto access to a LLIN [23].

The context may partially explain this finding: the study took place at the end of the malaria transmission season, a LLIN distribution campaign had recently been carried out, and recent information and sensitization campaigns were taking place as part of the *RooPfs* trial [20]. Also the trial setting may have had associated behavioural effects. The high usage estimate was also found in the main

trial study, in which 93.9% of children living in houses enrolled in the trial were reported to have slept under an LLIN (Pinder et al. pers. commun.). Even though this latter figure referred to children and was obtained via a direct questionnaire to their caretaker, it suggests high usage in this setting.

Though the finding of high bed net usage is plausible given the context, this study has four important limitations in terms of generalizability: (1) the study lacked any evidence-based method for validating responses (i.e., direct observation); (2) the study took place in an area where a great deal of health research had already taken place, opening the door to the possibility that our population was not representative of West Africa or even The Gambia especially since they had already been sensitized to malaria-related issues given their participation in the housing improvement trial; (3) though the sample size was sufficient for an overall assessment of bed net coverage based on a two-group comparison, there was not sufficient statistical power to identify the potential determinants of bed net use, such as ethnicity, age, or socio-economic status; and (4) there were no responses with the minimum (0 "yes" items) or maximum (4 or 5 "yes" items, depending on the arm) affirmations, suggesting that there may have been some unanticipated biases despite the method.

This final point merits further exploration. A potential cause of edge-avoidance in responses may be the consequence of poor item selection (i.e., items which did not provoke heterogeneity in responses). This is unlikely given that all four non-experimental items were chosen with the intention of neither being universal nor universally avoided. A more likely cause is that the list randomization method itself may not be an effective elicitation tool in certain contexts. Haber and colleagues, who also used the technique of having respondents finger-count affirmative items behind their back, found that list randomization did not correlate strongly with known ground-truth, and actually performed worse than direct questioning in some areas [17]. This is consistent with the findings by Arentoft and colleagues that list randomization did not result in higher frequencies of socially-sensitive behaviour reports compared to direct questioning [24]. Arentoft suggests that the reason for unexpectedly low affirmative responses to list randomization questionnaires might be that some participants may detect the "quasi-covert nature" of the study; Haber's main hypothesis explaining poor list randomization is "cognitive difficulty"—that is, the unusual and non-physical nature of tallying up responses may be confusing. Both of these factors may have contributed to this study's high usage finding. In regards to edge-avoidance, it may simply be

the case that participants did not want to reveal item-specific responses to *any* of the behaviours. Since an all “yes” or all “no” questionnaire means each item-specific response is known to the interviewer, participants may have gravitated towards non-edge responses so as to obscure all items. This is consistent with the fact that edge-avoidance took place in the experimental arm and the non-experimental arm (i.e., those administered the questionnaire without the bed net item).

Unlike HIV status [17, 24], which can be validated via laboratory test, the nature of sleeping under a LLIN makes ground-truth validation unfeasible. Even if study participants consented to being observed directly while sleeping (via camera or direct observation), this would undoubtedly introduce an even greater degree of social desirability bias, not to mention important concerns about privacy. A movement logger could theoretically be used as a less invasive and more accurate validation tool, but the awareness of the logger itself might also bias results, since one can assume that an individual is more likely to use an LLIN if they know their use is being monitored. Though list randomization is administratively complicated and subject to biases, it is a method which merits further research since alternatives—direct questioning, direct observation, mechanical monitoring—are subject to perhaps greater biases. For the question of LLIN usage, future research using the list randomization method should be directed in two areas: (1) to validate the method itself by (a) attempting an objective validation, (b) gauging seasonal variability in responses and (c) reproducing in other contexts, particularly where bed nets use has lower tradition than in The Gambia and far in time from recent bed net distributions; and (2) to better understand the possible social or cognitive biases that might explain edge-avoidance in responses.

Conclusion

List randomization offers a novel approach for exploring LLIN use in study communities, since the use of a LLIN can be considered a socially desirable behaviour and, therefore, subject to social desirability bias. The results of this list randomization experiment suggest very high LLIN usage among household heads in a rural area of a region of The Gambia with high coverage. High usage in a context of high coverage would be good news for public health practitioners worried about disuse and misuse, and is consistent with previous research showing high LLIN use following distribution campaigns [25–27]. Though list randomization has been shown to be a useful tool for eliciting sensitive behaviours in other contexts, for the specific case of LLIN usage further research is needed.

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Authors' contributions

JB analyzed the data pertaining to list randomization. MP, UD, SL, CJ, and ES contributed to study design, interpretation of the analysis, contextualization, and the writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during this study are not publicly available since they include identifiable protected health information of a sensitive nature. Researchers interested in accessing the data can contact the authors, to put them in contact with the ethics committee of the Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, PO Box 273, Banjul, The Gambia and will facilitate access to the data in the case of ethical approval being obtained.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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7. Study 4: A systematic review of the incremental costs of implementing a new vaccine in the expanded program of immunization in Sub-Saharan Africa

A Systematic Review of the Incremental Costs of Implementing a New Vaccine in the Expanded Program of Immunization in Sub-Saharan Africa

Joe Brew and Christophe Sauboin

Background. The World Health Organization is planning a pilot introduction of a new malaria vaccine in three sub-Saharan African countries. To inform considerations about including a new vaccine in the vaccination program of those and other countries, estimates from the scientific literature of the incremental costs of doing so are important.

Methods. A systematic review of scientific studies reporting the costs of recent vaccine programs in sub-Saharan countries was performed. The focus was to obtain from each study an estimate of the cost per dose of vaccine administered excluding the acquisition cost of the vaccine and wastage. Studies published between 2000 and 2018 and indexed on PubMed could be included and results were standardized to 2015 US dollars (US\$). **Results.** After successive screening of 2119 titles, and 941 abstracts, 58 studies with 80 data points (combinations of country, vaccine type, and vaccination approach—routine v. campaign) were retained. Most studies used the so-called ingredients approach as costing method combining field data collection with documented unit prices per cost item. The categorization of cost items and the extent of detailed reporting varied widely. Across the studies, the mean and median cost per dose administered was US\$1.68 and US\$0.88 with an interquartile range of US\$0.54 to US\$2.31. Routine vaccination was more costly than campaigns, with mean cost per dose of US\$1.99 and US\$0.88, respectively. **Conclusion.** Across the studies, there was huge variation in the cost per dose delivered, between and within countries, even in studies using consistent data collection tools and analysis methods, and including many health facilities. For planning purposes, the interquartile range of US\$0.54 to US\$2.31 may be a sufficiently precise estimate.

Keywords

costs, malaria vaccine, sub-Saharan Africa, systematic literature review, vaccine programs

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Introduction

When contemplating introduction of a new health care intervention for the first time, an accurate estimation of its full costs based on real-world data will usually not be available. Whereas it is increasingly recognized that rational decision making on the allocation of health care resources requires comprehensive assessments of the outcomes and benefits as well as the costs of interventions, it may be necessary to base decisions on provisional,

approximate data.^{1,2} One approach to resolve this dilemma is to examine the costs of interventions that are similar to the one under consideration and which have already been implemented in the jurisdiction of interest or elsewhere.^{1,2}

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A case in point is the newly developed RTS,S vaccine candidate against malaria, which is considered for introduction in several African sub-Saharan countries, where the disease burden of malaria is still heavy. Despite sustained progress in the fight against malaria with an estimated decrease in malaria deaths worldwide of 60% since 2000, estimations from the World Health Organization (WHO) indicate that around 438,000 individuals died of malaria in 2015.³ More than 90% of these deaths occurred in sub-Saharan Africa and most of them were children under the age of 5 years.

The RTS,S vaccine candidate received a positive evaluation by the European regulatory authorities and WHO is planning to conduct a pilot implementation of the vaccine in three sub-Saharan countries with moderate to high malaria transmission intensity.³ To inform the consideration about including the RTS,S vaccine candidate as part of the Expanded Program on Immunization of these countries, estimates of the anticipated incremental costs of doing so are highly relevant and important.⁴

The purpose of this study was to have a clear overview of the methods and estimates for vaccine implementation costs from the scientific literature. This review supports the design and allows comparison with results obtained from a field study conducted in five African sub-Saharan countries (Burkina Faso, Ghana, Kenya, Mozambique, and Tanzania) to derive an estimate of the anticipated costs of introducing the RTS,S vaccine candidate in sub-Saharan countries. This field study is described in the accompanying paper.⁵ This review of the literature focuses on studies reporting the costs of recent vaccine programs in these countries. Ideally, such studies should be using micro-costing principles with itemized costs and separate reporting of quantities of resources and their unit prices. However, relatively few studies based on these principles have been published until now, although the importance of using this approach is increasingly

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recognized and guidelines for their performance, reporting, and appraisal are under preparation.^{6,7} We grant that the scarcity of studies in this area may be somewhat a function of our limited search (we used only one database). We therefore applied less strict criteria for inclusion of studies, but at minimum, studies should report itemized costs or a cost per dose delivered to be selected. Further inclusion criteria are detailed in the next section.

Methods

Systematic Search Strategy

PubMed was searched for relevant articles published between 2000 and the end of 2018 using the following search string:

(((((vaccine OR vaccination) OR immunization) AND (economic OR cost)) AND ("2000/1/1"[Date - Publication]: "2018/12/31"[Date - Publication]))) AND (Africa OR country x). The countries specified were Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, The Democratic Republic of Congo, Côte d'Ivoire/Ivory Coast, Djibouti, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Rwanda, Senegal, Sierra Leone, Somalia, Sudan, Tanzania, Togo, Uganda, Zambia, and Zimbabwe.

Screening

First, the title of the identified articles was screened, then the abstract of the retained possibly relevant articles, and finally the full text of papers retained after the two screening steps. The reference lists of the retained articles for full text screening were also examined and possibly relevant ones included in the screening steps. Papers were excluded if they specifically focused on non-GAVI (Global Alliance for Vaccines and Immunization) or non-African countries, if they were about nonhuman vaccines, and if they were written in languages other than English and French.

The criteria for selection of articles were: 1) costing study performed in a GAVI-supported sub-Saharan African country (or more than one) in order to have a more homogeneous set of countries in terms of income level and health system status; 2) study performed between 2000 and 2018; 3) costing performed for a human vaccine; 4) costs itemized and quantified; itemized costs reported in monetary terms or as percentages of an overall cost figure reported in monetary terms; and

5) possibility to calculate a comprehensive cost per dose administered, excluding the costs of vaccine.

Data Extraction

The data extracted from each selected study include the authors' report of the costs of vaccination per dose. If the cost per dose was presented in the article, this figure was used as such. If the reported cost figure included the cost of the vaccine, we subtracted the vaccine cost from this or the proportion of non-vaccine costs in the total costs was applied. If a study reported the cost per fully vaccinated child (FVC), this figure was divided by the number of doses required for a FVC and, if necessary, the cost of the vaccine was deducted as well. For studies reporting detailed, itemized costs, the cost per dose was calculated as the sum of the itemized costs excluding the costs of vaccine and wastage. We did not have an a priori definition for wastage, and took wastage as the value defined by the study authors. In one particular case, the study reported a cost figure calculated as the weighted average of administration in urban and rural facilities based on the number of facilities of the respective type.⁸ For this study, we recalculated the cost per dose using the weighted average of the number of doses administered in urban versus rural facilities.

Categorization

For cost items, the following categories were used and their proportion of the total cost per dose calculated to the extent possible: human resources, transportation, administration, equipment, sensitization, training, and surveillance. Explicit definitions for each category were not created; instead, we "agnostically" relied on the definitions used by authors themselves, and used common sense for classifying those expenditures that did not use the same jargon as our categories (e.g., "awareness" was classified as "sensitization," "salaries" were classified as "human resources," etc.). These categories were used to follow an approach similar to the one developed for the field study as described in the accompanying paper.

Perspective and Challenges

We only took into account the cost from the program/providers' perspective. Though this excludes a great deal of the true economic cost of vaccine programs, this limited perspective is most relevant to the aim of this study, and most applicable to estimating potential program costs for the rollout of an intervention.

If incremental or marginal costs were mentioned in a study, that figure was preferably used rather than an average economic cost per dose in order to account for the actual budgetary requirement for the introduction of a new vaccine in the program. Though incremental costs are more variable and are highly contingent on local capacity, this approach was in line with our study's aim than looking at full economic program costs. However, distinctions between cost types such as fixed and variable, start-up, and recurrent were not retained, because they were used inconsistently across studies, sometimes overlapping, sometimes insufficiently categorized, and sometimes in incompatible ways.

Some studies do not specify the vaccine purchase cost separately but combine it with injection material and other supplies. In such cases, we decided to eliminate the entire cost item including both vaccine and injection material costs, given that the costs of injection supplies generally are small compared with the vaccine purchase cost. Some studies do not explicitly mention the vaccine price,^{9–13} but they may mention the source of data; in such cases, we retrieved it from the data source, mostly the UNICEF website.¹⁴

In other situations, it was not possible to remove the cost of wastage because it was not separately reported in the study and was therefore a nonobserved component of the final cost. If a study reported wastage separately, this item was not included in our calculation of the cost per dose.

Wastage is a major cost that is included in most studies but not always based on field data and often included in the vaccine cost and not reported separately. Wastage costs may be very high according to some studies^{12,15} and there are several difficulties involved in handling them. Wastage costs depend mainly on the vaccine price and the level of the health care system at which the wastage occurs, with variation between routine vaccinations in health facilities and outreach activities or vaccination campaigns. Wastage also varies with the number of doses per vial, the service volume in terms of number of vaccinations administered, and the vaccine characteristics. As a consequence, the costs related to wastage vary widely and may be difficult to capture fully. For these reasons we did not include wastage as a separate cost category in the cost estimation.

Monetary Homogenization

All the studies report costs in US dollars (US\$) for a base year, usually the year the cost data were collected. All the cost figures were converted to 2015 US\$ using

data from the World Bank.¹⁶ This conversion was performed in 3 steps: 1) conversion from US\$ to the local currency unit (LCU) for the base year reported in the study; 2) taking inflation into account by applying the consumer price index increase in the LCU from the base year until and including 2015; and 3) converting the inflation corrected figure back to 2015 US\$. The search query was devised by CS. The initial search was carried out by JB; iterative screening was carried out by both JB and CS.

Results

Screening Results

The process of articles selection is summarized in Figure 1 with details on the reasons for exclusion. The initial search returned 2119 articles. Based on the title alone, 941 were retained and 1178 were eliminated for one of the following reasons (from the most to least common reason): 1) no or insufficient economic content, 2) not vaccination of humans, 3) not about a vaccine, 4) not about an African GAVI country, 5) article withdrawn, or 6) not in English or French.

The abstract of the 941 retained articles were read, and based on this, 778 articles were excluded for one of the following reasons (from the most to least common reason): 1) no cost researched, retrieved, reported or not in relation with vaccine administration; 2) cost not related to vaccine delivery or was for delivery in a specific emergency context; 3) no abstract found or not in English/French or article withdrawn; 4) not vaccination in humans; 5) not in African GAVI country; 6) vaccination of special subgroups not including children; 7) opinion paper, review, qualitative study, meeting report; or 8) not about a vaccine.

The remaining 163 articles were screened based on the full text and 108 were excluded based on one of the following reasons (from the most to least common reason): 1) referring to another article (added or already included in the articles reviewed), 2) no delivery cost or no doses reported, 3) limited to specific cost items (often injection or logistics), 4) based on assumptions or models only, 5) special vaccination context (e.g., refugees, outbreak, emergency), 6) referring to another article that could not be found/included, 7) not in African country, 8) the vaccine price could not be segregated from the cost, or 9) data not available or accessible in journal supplement.

In addition to the 55 articles selected by this procedure, three more were included after examination of eight articles found in the reference lists of selected articles. The other five were excluded because they focused on special

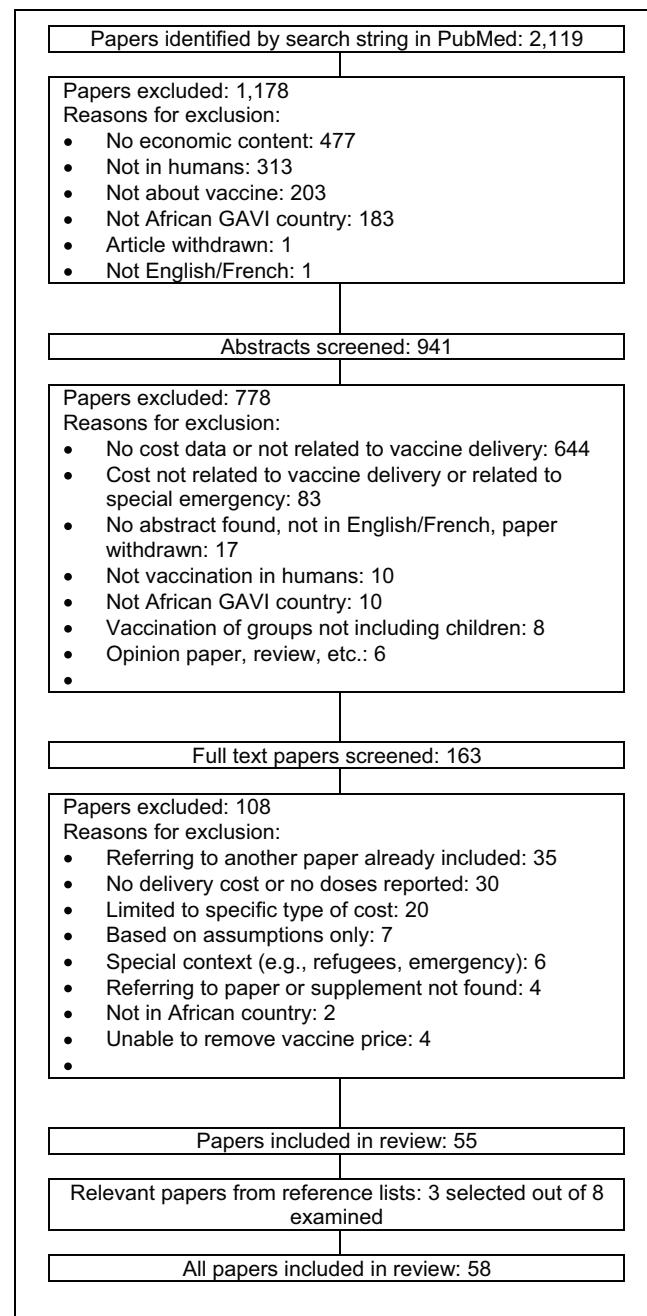


Figure 1 Selection of articles.

GAVI, Global Alliance for Vaccines and Immunization.

emergency situations (2), only logistics costs (1), or did not allow elimination of the vaccine purchase cost (1).

The 58 articles contained 80 data points, that is, combinations of country, vaccine type, and vaccination approach (routine or campaign). The 22 countries included had a preponderance of East African countries, and the most

frequently represented were Tanzania (9/80), Uganda (9), Zambia (8), Ethiopia (7), Ghana (6), Kenya (4), and Burkina Faso (4). One study aggregated data for 27 African countries,¹⁷ and another one aggregated data on HPV immunization for 10 African countries.¹⁸

Altogether 11 different vaccines including a category defined as “multiple vaccines” when vaccines could not be distinguished were examined, and those costed in the 58 data points on routine vaccination were multiple vaccines (17), measles (8), malaria (8), rotavirus (7), human papillomavirus (HPV; 8), hepatitis B virus (HBV; 5), pneumococcal conjugate vaccine (PCV; 4), and meningitis (1). The vaccines included in the 22 data points for campaign-type vaccination were predominantly measles (8), cholera (7), and meningitis (3), with the remaining including typhoid, yellow fever, and multiple vaccines.

Most studies used the so-called ingredients approach as costing method, combining field data collection with documented unit prices for each cost item. One clear example of this is the EPIC (Extended Program of Immunization Costing and Financing) project, which collected data for routine vaccination cost using the same consistent methods in around 50 vaccine delivery facilities in each of four African GAVI countries (and two non-African).^{8,19,20} Of the 80 data points, 55 (69%) are based on primary cost data collected in field studies, with some variation in the extent of field data collection and in some cases limited to interviews with health workers.

For a minority of studies,^{17,20–25} the costing is based on existing budget plans (such as comprehensive multi-year plans (cMYP) or financial plans for immunization of the Ministry of Health). An average cost of administration is then calculated based on the total cost and the number of doses planned. One study in Nigeria²⁶ is based on the cost of administration estimated in a study in Tanzania,²⁷ with an adaptation limited to the difference in purchasing power.

Several studies of vaccination campaigns are based on all the costs incurred over a relatively short time period in the campaign and recorded in financial accounts or reports on the campaign.^{28–33}

A number of studies are actually mainly cost-effectiveness analyses just reporting the cost of vaccination used as an input, sometimes based on primary collection of field data.^{9,21,24,25,34–41} The initial PubMed search returned several more cost-effectiveness studies but these were excluded because they based their cost estimates on cost data from papers included in the review. The cost-effectiveness analyses retained in the review have either collected primary cost data or are based on other studies.

Analysis

The studies are summarized in Table 1 with a brief indication of the methods used by the authors for the cost estimation and the estimated average cost per dose in 2015 US\$. All the costs extracted are estimated from the perspective of the public health authorities.

The aggregate cost results are summarized in Table 2, with overall average and median cost per dose of US\$1.68 and US\$0.88, respectively, and a range from US\$0.16 to US\$13.58. For routine vaccinations, the average and median cost per dose are US\$1.99 and US\$1.17, respectively, and for campaign-type vaccinations US\$0.88 and US\$0.66, respectively. The histogram in Figure 2 shows the distribution of cost results in intervals of US\$0.25. For both types of vaccination approach, the major part of the average cost results is in the interval US\$0.25 to US\$1.50, with 33/58 of the routine vaccination studies and 20/22 of the campaign-type studies.

The cost per dose varies with the type of vaccine as shown in Table 3. HPV is an outlier with average and median costs of US\$5.20 and US\$3.84, respectively, for routine vaccinations, far above the corresponding cost figures for other routine vaccination programs. These aggregates are very much determined by a single study in Mali with a cost of US\$13.58,⁴² but even disregarding that study the costs are high, with a range of average costs for the remaining five HPV studies from US\$1.18⁴³ to US\$5.21.²⁶ A multi-country study found an average cost of US\$8.30 per dose administered.¹⁸ The reason for the elevated costs may be that HPV vaccines are typically delivered through a bundling with school-based or outreach programs, which require more training and personnel. If HPV vaccinations are excluded from the aggregation, the average cost for routine programs would be US\$1.47 instead of US\$1.99.

There was a tendency for the newer studies to be more comprehensive including further cost categories such as the costs of social mobilization/sensitization and surveillance programs. The results regarding the proportion of the total cost per dose accounted for by each cost category are based on the studies for which these data were available. Sixteen of the 58 articles do not report any data on cost categories,^{9,22,23,25,28,35,37,38,40,41,44–49} and one study only provides details on transportation, representing 17% of the total cost per dose.⁵⁰ Table 4 presents the number of data points for each cost category and its average proportion of the cost per dose based on the available data (Note: the average proportions are not supposed to sum to 100 across the cost categories due to the gaps in the reporting of categories). Human resources and transportation are the most frequently reported

(text continues on p. 12)

Table 1 Summary Table of Costing Studies, Cost per Dose in 2015 US Dollars

Author, Year	Title	Disease	Country	Type of Study	Year of Data	Campaign/ Routine	Cost, 2015 US Dollars
Edmunds, 2000 ¹²	The cost of integrating hepatitis B virus vaccine into national immunization programs: a case study from Addis Ababa	HBV	Ethiopia	Survey and ingredients approach	1994–1995	Routine	0.63
Edmunds, 2000 ¹²	The cost of integrating hepatitis B virus vaccine into national immunization programs: a case study from Addis Ababa	Multiple	Ethiopia	Survey and ingredients approach	1994–1995	Routine	1.03
du Châtelet, 2001 ²⁸	Comparison of cost-effectiveness of preventive and reactive mass immunization campaigns against meningococcal meningitis in West Africa: a theoretical modeling analysis	Multiple	Senegal/West Africa	Survey from financial accounts—ingredients method	1997	Campaign	0.66
Dayan, 2004 ²¹	Cost-effectiveness of three different vaccination strategies against measles in Zambian children	Measles	Zambia	Based on Ministry of Health (MoH) report of cost allocation	2000	Routine Campaign	0.84 0.56
Nanyunja, 2003 ³⁴	Impact of mass measles campaigns among children less than 5 years old in Uganda	Measles	Uganda	Based on total costs of supplies and operation (no more precision)	2000	Campaign	0.66
da Silva, 2003 ³⁹	Évaluation des coûts opérationnels d'une campagne de masse préventive contre la méningite à méningocoque et la fièvre jaune au Sénégal, en 1997	Meningitis	Senegal	Field survey during the campaign	1997	Campaign	0.40
Cavailler, 2006 ³⁰	Feasibility of a mass vaccination campaign using a two-dose oral cholera vaccine in an urban cholera-endemic setting in Mozambique	Cholera	Mozambique	Field survey during the campaign	2003–2004	Campaign	1.41
Griffiths, 2005 ³⁴	The cost-effectiveness of introducing hepatitis B vaccine into infant immunization services in Mozambique	Hepatitis B	Mozambique	Ingredients approach, data collected from central EPI office	Not specified	Routine	2.36
Kim, 2007 ³⁵	Economic evaluation of hepatitis B vaccination in low-income countries: using cost-effectiveness affordability curves	Hepatitis B	Gambia	Described in technical appendix that has been requested	Not specified	Routine	0.74
Levin, 2007 ⁵⁰	An economic evaluation of thermostable vaccines in Cambodia, Ghana, and Bangladesh	Multiple	Ghana	Ingredients approach based on data collected through questionnaire with key informants ²¹	2001	Routine	0.62

(continued)

Table 1 (continued)

Author, Year	Title	Disease	Country	Type of Study	Year of Data	Campaign/ Routine	Cost, 2015 US Dollars
Le Gargasson, 2015 ^g	Costs of routine immunization and the introduction of new and underutilized vaccines in Ghana	Multiple	Ghana	Survey with random sampling at facility level and analysis of expenditure records with resource utilization	2010	Routine	1.63
Schütte, 2015 ⁸	Cost analysis of routine immunization in Zambia	Multiple	Zambia	Survey with random sampling of facilities and questionnaire for interviews	2011	Routine	2.63
Brenzel, 2015 ¹⁷	Costs and financing of routine immunization: Approach and findings of a multi-country study (EPIC)	Multiple	Multiple low income	Analysis by extracting country-level information from comprehensive multi- year plans (cMYP) Analysis based on data from the country multi-year plan (cMYP)	2008–2011	Routine	2.12
Kim, 2010 ²²	Economic evaluation of pneumococcal conjugate vaccination in The Gambia	PCV	Gambia	Cost estimates based on previously published studies	2005 (year of currency)	Routine	0.37
Klingler, 2012 ³⁶	Cost-effectiveness analysis of an additional birth dose of hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique	Hepatitis B	Mozambique	Cost estimates based on previously published studies	2008 (year of currency)	Routine	0.41
Levin, 2013 ⁴³	Delivery cost of human papillomavirus vaccination of young adolescent girls in Peru, Uganda, and Viet Nam	HPV	Uganda	Ingredients-based approach based on data collected at facility level (questionnaire)	2008–2010	Routine	1.18
Geng, 2017 ²⁰	The cost structure of routine infant immunization services: a systematic analysis of six countries	Multiple	Benin (B) Ghana (G) Uganda (U) Zambia (Z) Cameroon	Survey with random sampling of facilities and questionnaire for interviews (EPIC database)	2011	Routine	B: 0.77 G: 2.67 U: 1.29 Z: 2.29
Waters, 2004 ⁴⁵	Coverage and costs of childhood immunizations in Cameroon	Multiple	Ethiopia	Survey and average costing approach	2001–2002	Routine	1.15
Fiedler, 2008 ¹⁰	The cost of child health days: a case study of Ethiopia's enhanced outreach strategy (EOS)	Measles	Ethiopia	Activity-based costing and ingredients approach	2006	Campaign	0.60
Tate, 2009 ³⁷	Rotavirus disease burden and impact and cost-effectiveness of a rotavirus vaccination program in Kenya	Rotavirus	Kenya	WHO costing model	Model	Routine	0.78
Bishai, 2011 ³⁸	The cost-effectiveness of supplementary immunization activities for measles: A stochastic model for Uganda	Measles	Uganda	External references	2003; 2006; 2007	Routine Campaign	2.08 1.23

(continued)

Table 1 (continued)

Author, Year	Title	Disease	Country	Type of Study	Year of Data	Campaign/ Routine	Cost, 2015 US Dollars
Babigumira, 2011 ⁹	Assessing the cost-effectiveness of measles elimination in Uganda: Local impact of a global eradication program	Measles	Uganda	Survey and ingredients approach	2003; 2006; 2009	Routine Campaign	4.27 2.09
Levin, 2011 ¹¹	Global eradication of measles: An epidemiologic and economic evaluation	Measles	Ethiopia	Average costing and ingredients approach	Not specified	Routine Campaign	2.08 0.80
Colombini, 2011 ²³	Costs and impact of meningitis epidemics for the public health system in Burkina Faso	Meningitis	Burkina Faso	Real spending method and the ingredients method	2007	Campaign	0.65
Schaetti, 2012 ²⁶	Costs of illness due to cholera, costs of immunization, and cost-effectiveness of an oral cholera mass vaccination campaign in Zanzibar	Cholera	Zanzibar	Reference	Not specified	Campaign	3.42
Quentin, 2012 ²⁷	Costs of delivering human papillomavirus vaccination to schoolgirls in Mwanza Region, Tanzania	HPV	Tanzania	Top-down analysis of project costs and interviews	2011–2015	Routine	3.28
Sume, 2013 ⁴⁷	A locally initiated and executed measles outbreak response immunization campaign in the nylon health district, Douala Cameroon 2011	Measles	Cameroon	Costs based on ingredients approach	2011	Campaign	0.20
Ayieko, 2013 ⁴⁸	Assessment of health benefits and cost-effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccination in Kenyan children	PCV	Kenya	Costs based on actual capital costs and recurrent spending	2008–2010	Routine	0.20
Tracy, 2014 ⁴²	Planning for human papillomavirus (HPV) vaccination in sub-Saharan Africa: A modeling-based approach	HPV	Mali	Ingredients approach	2006–2011	Routine	13.58
Carias, 2015 ⁴⁹	Economic evaluation of typhoid vaccination in a prolonged typhoid outbreak setting: the case of Kasese district in Uganda	Typhoid	Uganda	Ingredients approach	Not specified	Campaign	0.18
Ruhago, 2015 ³	Cost-effectiveness of live oral attenuated human rotavirus vaccine in Tanzania	Rotavirus	Tanzania	Average costing	2011–2012	Routine	4.13

(continued)

Table 1 (continued)

Author, Year	Title	Disease	Country	Type of Study	Year of Data	Campaign/	Cost, 2015 US
						Routine	Routine
Kaucley, 2015 ³⁵	Cost-effectiveness analysis of routine immunization and supplementary immunization activity for measles in a health district of Benin	Measles	Benin	Average cost for capital costs and ingredients approach for recurrent costs	2011	Routine	2.62 0.84
Colombini, 2015 ²³	Costs of <i>Neisseria meningitidis</i> group A disease and economic impact of vaccination in Burkina Faso	Meningitis	Burkina Faso	Average cost based on cMYP 2011	2011	Routine	0.33 0.28
Galaktionova, 2015 ⁴	Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data	Malaria	Burkina Faso (BF) Ghana (G) Kenya (K) Senegal (S) Tanzania (T) Uganda (U) Malawi	Ingredients approach	Not specified	Routine	BF: 0.37 G: 0.94 K: 0.69 S: 0.43 T: 0.34 U: 0.46
Bar-Zeev, 2016 ⁴⁰	Cost-effectiveness of monovalent rotavirus vaccination of infants in Malawi: A postintroduction analysis using individual patient-level costing data	Rotavirus		Average costs based on cMYP Not specified	Not specified	Routine	0.60
Umeh, 2016 ²⁶	Mothers' willingness to pay for HPV vaccines in Anambra state, Nigeria: A cross sectional contingent valuation study	HPV	Nigeria	Based on data from Tanzania and adjusted to Nigeria with purchasing power	Not specified	Routine	5.21
Byberg, 2017 ⁴¹	Cost-effectiveness of providing measles vaccination to all children in Guinea-Bissau	Measles	Guinea-Bissau	Based on unit costs for supplies and assuming no staff nor equipment cost	Not specified	Routine	0.82
Doshi, 2017 ²⁴	Assessing the cost-effectiveness of different measles vaccination strategies for children in the Democratic Republic of Congo	Measles	Congo	Based on budget documents and additional literature-based references	2013	Routine	0.92 1.45
Ilboudo, 2017 ³¹	Delivery cost analysis of a reactive mass cholera vaccination campaign: a case study of Shanchol vaccine use in Lake Chilwa, Malawi	Cholera	Malawi	Based on the financial reports of the campaign and average costing approach	2016–2017	Campaign	0.55
Poncin, 2017 ³²	Implementation research: Reactive mass vaccination with single-dose oral cholera vaccine, Zambia	Cholera	Zambia	Based on the financial reports of the campaign and average costing approach	Not specified	Campaign	0.29

(continued)

Table 1 (continued)

Author, Year	Title	Disease	Country	Type of Study	Year of Data	Campaign/ Routine	Cost, 2015 US Dollars
Griffiths, 2016 ⁵⁵	Costs of introducing pneumococcal, rotavirus, and a second dose of measles vaccine into the Zambian immunization program: Are expansions sustainable?	PCV, rotavirus, measles	Zambia	Ingredients based (EPIC)	Not specified	Routine	Measles: 5.76 PCV: 2.42 Rota: 3.21
Ciglenecki, 2013 ⁵⁵	Feasibility of mass vaccination campaign with oral cholera vaccines in response to an outbreak in Guinea	Cholera	Guinea	Costs based on actual capital costs and recurrent spending	2012	Campaign	1.44
Douba, 2011 ⁵⁶	Estimated costs of the expanded program of immunization in the health district of Grand Bassam, Côte d'Ivoire	Multiple	Côte d'Ivoire	Survey and average costing approach	2006	Routine	2.82
Ebong, 2001 ⁵⁷	Impact of the introduction of new vaccines and vaccine wastage rate on the cost-effectiveness of routine EPI: Lessons from a descriptive study in a Cameroonian health district	Multiple	Cameroon	Survey and ingredients approach	2009	Routine	0.95
Garcia, 2013 ⁵⁸	Comparative cost models of a liquid nitrogen vapor phase (LNVP) cold chain-distributed cryopreserved malaria vaccine versus a conventional vaccine	Multiple	Tanzania	Costs based on ingredients approach	2011	Routine	4.96
Griffiths, 2009 ⁵⁹	Incremental system costs of introducing combined DTwP-hepatitis B-Hib vaccine into national immunization services in Ethiopia	Hepatitis B	Ethiopia	Interviews with key informants at all levels of the health system	2007	Routine	0.59
Hutton, 2006 ⁶⁰	The costs of introducing a malaria vaccine through the expanded program on immunization in Tanzania	Malaria	Tanzania	Ingredient costs approach based on MoH reports	2000–2002	Routine	0.50
Hutubessy, 2012 ⁶¹	A case study using the United Republic of Tanzania: costing nationwide HPV vaccine delivery using the WHO Cervical Cancer Prevention and Control Costing Tool	HPV	Tanzania	WHO C4P tool	2011–2015	Routine	2.98
Levin, 2001 ⁶²	Case study on the costs and financing of immunization services in Ghana	Multiple	Ghana	Survey and average costing approach	2000	Routine Campaign	0.74 0.37

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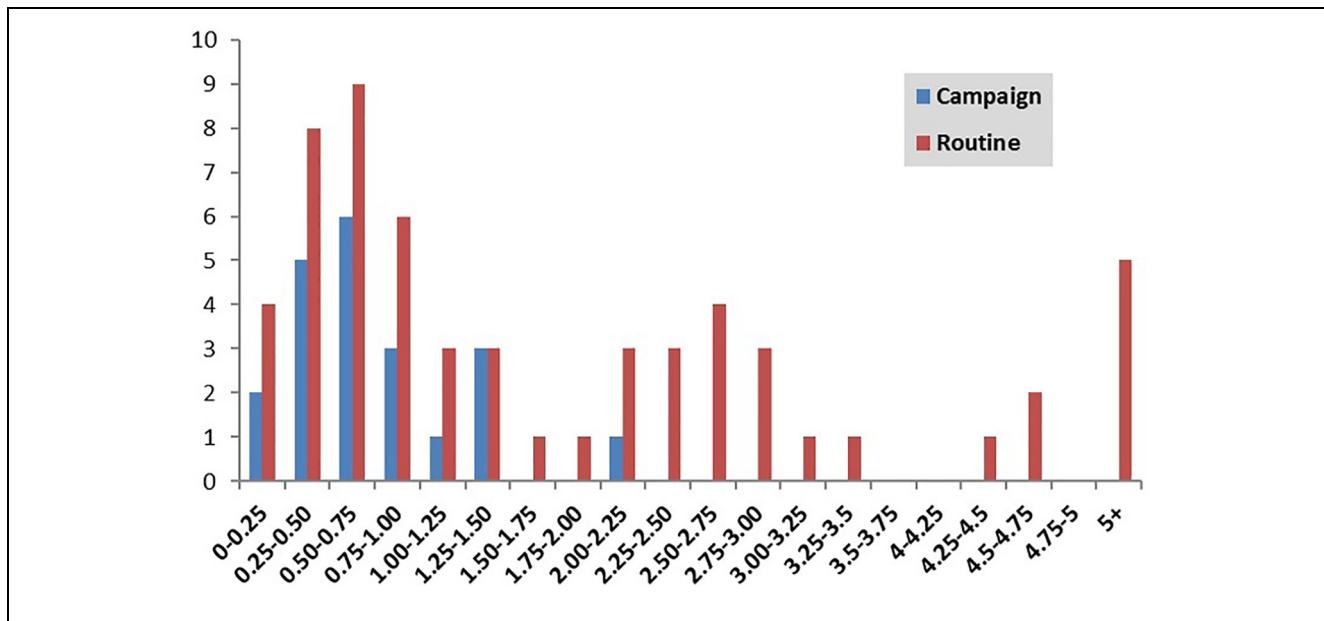
Table 1 (continued)

Author, Year	Title	Disease	Country	Type of Study	Year of Data	Campaign/ Routine	Cost, 2015 US Dollars
Madsen, 2014 ⁶³	Estimating the costs of implementing the rotavirus vaccine in the national immunization program: The case of Malawi	Rotavirus	Malawi	Ingredients approach	2009–2011	Routine	1.78
Mvundura, 2015 ⁶⁴	Estimating the costs of the vaccine supply chain and service delivery for selected districts in Kenya and Tanzania	Multiple	Kenya (K) Tanzania (T)	Ingredients-based costing method using data collected at facility-level with standardized questionnaires	2012	Routine	K: 1.46 T: 2.89
Ngabo, 2015 ⁶⁵	A cost comparison of introducing rotavirus and human papillomavirus vaccines in Rwanda	PCV, rotavirus, HPV	Rwanda	Primary and secondary data collection and using WHO C4P tool	Not specified	Routine	PCV: 0.23 Rota: 0.16 HPV: 4.40
Tediosi, 2009 ⁶⁶	Simulation of the cost-effectiveness of malaria vaccines	Malaria	Tanzania	Ingredients approach	Not specified	Routine	1.41
Usuf, 2014 ⁶⁷	Costs of vaccine delivery in the Gambia before and after pentavalent and pneumococcal conjugate vaccine introductions	Multiple	Gambia	Survey at facility level with tally sheet and questionnaire	2009 (year of currency)	Routine	0.21
Zengbe-Acra, 2009 ⁶⁸	Estimated operational costs of vaccination campaign to combat yellow fever in Abidjan	Yellow fever	Côte d'Ivoire	Survey and average costing approach	2001	Campaign	0.41
Hilde, 2018 ⁶⁹	Cost of a human papillomavirus vaccination project, Zimbabwe	HPV	Zimbabwe	Retrospective ingredients-based approach	2014–2016	Routine	2.67
Pecenka, 2018 ²⁵	Reevaluating the cost and cost-effectiveness of rotavirus vaccination in Bangladesh, Ghana, and Malawi: A comparison of three rotavirus vaccines	Rotavirus	Malawi	Based on cMYP 2010–2014	2010	Routine	0.29
Teshome, 2018 ³³	Feasibility and costs of a targeted cholera vaccination campaign in Ethiopia	Cholera	Ethiopia	Retrospective micro-costing approach based on field interviews	2015	Campaign	0.68
Botwright, 2017 ⁸	Experiences of operational costs of HPV vaccine delivery strategies in GAVI-supported demonstration projects	HPV	Multi-country	Cross-sectional retrospective cost estimates generated by the C4P tool	2013–2016	Routine	8.30

cMYP, comprehensive multi-year plan; EPI, Expanded Program on Immunization; EPIC, Extended Program of Immunization Costing and Financing; GAVI, Global Alliance for Vaccines and Immunization; Hib, *Haemophilus influenzae* type B; PCV, pneumococcal conjugate vaccine; WHO, World Health Organization.

Table 2 Summary of Cost per Dose Delivered

	Average	Median	Lower Quartile	Upper Quartile
Overall	1.68	0.88	0.54	2.31
Routine	1.99	1.17	0.59	2.66
Campaign	0.88	0.66	0.40	1.13

**Figure 2** Number of data points reporting average cost in cost intervals of US\$ 0.25.**Table 3** Cost per Dose Delivered for Different Types of Vaccine, 2015 US\$

	Average	Median
Multiple	1.65	1.29
HBV	0.95	0.63
Measles	1.73	1.08
Meningitis	0.41	0.36
Cholera	1.14	0.68
HPV	5.20	3.84
PCV	0.81	0.30
Malaria	0.64	0.48
Rotavirus	1.57	0.78
Typhoid	0.18	0.18
Yellow fever	0.41	0.41

HBV, hepatitis B vaccine; HPV, human papilloma virus; PCV, pneumococcal conjugate vaccine.

categories and surveillance the least. The average proportions vary somewhat between the vaccination approaches, in particular, for human resources, administration, and equipment. Overall, human resources account for almost half (44%) of the average cost per dose followed by administration, transportation, and building/equipment (each about 20%).

Discussion

This review and summary analysis of vaccination costing studies performed in sub-Saharan African countries shows that the estimated cost per dose (excluding vaccine and wastage costs) varies substantially across studies. Even though the costing methods used are fairly consistent, predominantly using an ingredients approach with

Table 4 Mean Proportion of Cost per Dose for Each Cost Category from the Studies Reporting Each Item

Category	Number of Data Points (Total = 56)			Average Share of the Cost Without Vaccine and Wastage ^a		
	Total	Routine	Campaign	Total	Routine	Campaign
Human resources	55	43	12	44%	47%	37%
Transportation	51	40	11	20%	20%	22%
Administration	45	34	11	20%	17%	27%
Equipment	38	30	8	18%	20%	12%
Sensitization	38	29	9	10%	10%	11%
Training	33	25	8	7%	8%	3%
Surveillance	11	9	2	5%	5%	5%

^aThe total exceeds 100% because the average share is calculated across studies which include the cost category.

data collection by questionnaires, interviews, or reports, the studies lack standardization with respect to which cost items are reported and how these are reported, so their findings are not easily comparable. We suspect that a large part of the variation in the estimated costs reflects differences in what is reported under each cost category.

It should be noted, however, that the largest study in our review using consistent methods and tools of data collection and cost estimation for approximately 50 health facilities in each of four sub-Saharan African countries also finds high variability between (and within) the countries with a more than threefold difference between the minimal and maximal cost per dose, that is, US\$0.77 in Benin and US\$2.67 in Ghana. The study authors consider that the estimated variation reflects real differences between the countries in unit prices, characteristics of the health systems, and in the practical organization of the vaccination programs.²⁰ Of note, the per capita income in Ghana is more than double that in Benin, the countries in that study with the highest and lowest cost per dose, respectively, so the unit costs of labor and other resources are much higher in Ghana.⁵¹

Across the studies, personnel costs amounted to approximately half the cost per dose. Labor time is a shared resource, which requires estimation of both the proportion of the time of each type of personnel to vaccination activities and within vaccination the allocation of time to different activities. Allocation of labor time is probably one of the cost categories most difficult to estimate reliably without direct observation, because respondents may be motivated to report a particular allocation of effort. Interestingly, the above-mentioned four-country study reports a substantial reduction of the labor cost per dose with an increasing vaccination activity (number of doses administered per time period), which suggests improving efficiency through economies of scale in the use of labor with rising vaccination

activity.²⁰ However, such a possible relationship has not been investigated in other studies in this review.

Our findings are similar to results reported by Portnoy et al.,⁵² which estimate the cost of vaccination programs in 94 low- and middle-income countries using model-based costs and cMYP planned budgets. The reported average cost per dose for routine and campaign delivery approaches in low income countries is (2010)US\$1.75 when the vaccine cost is excluded, similar to our average of (2015)US\$1.68 across the GAVI countries. Human resources cost categories are also identified as the most important but with a higher proportion (82%) than in our study, although this figure includes both low- and middle-income countries. Another recent review reports a range of the incremental economic cost for newly introduced vaccines (PCV and rotavirus vaccines) between (2016)US\$0.48 to US\$1.38 in Benin, Rwanda, and Uganda. These results are also close to our findings with means of (2015)US\$0.81 and US\$1.57 for these two vaccines.⁵³

Among the specific difficulties encountered in allocating costs into one of the categories we had predefined, were that some papers disclosed more details than the specified categories, for instance, reporting the cost of personnel time devoted to training; in such cases we had to choose the higher level category in which to allocate the cost. The reverse problem also occurred, where papers reported aggregated categories (e.g., transportation and equipment combined). In such cases we allocated the cost to the category expected to represent the highest cost. Another type of situation was that a category used in a study did not match the ones we selected. An example would be “cold chain,” which could either be part of the equipment (fridges) in a health facility or related to transportation of vaccines. In such cases we qualitatively based the cost allocation on elements of the text description in the paper.

We found that routine vaccination programs generally have higher reported costs than introduction campaigns even though some campaigns have very high human resources costs. The likely reasons for the lower cost of vaccination campaigns is that they require less capital investment in health facilities than routine vaccination, and/or capital investments are not considered into these studies. A further hypothesis is that this finding might be explained by a tendency for costing studies of routine vaccination programs to be thorough and comprehensive, whereas costing of campaigns or introduction programs perhaps tend to focus most on those costs that differed from routine programs. This somewhat counterintuitive finding could also be explained by the fact that studies did not generally report or describe differences in financial versus economic costs. Accordingly, we were unable to perform separate financial versus economic analyses. This, unfortunately, limits the generalizability of our study.

Authors more frequently reported incremental costs instead of average economic costs. Though this is helpful in determining the marginal cost of a hypothetical program to be rolled out, this also poses an important limitation to the applicability of our study: since incremental costs is highly contingent on local capacity and infrastructure, its variability is high, and its generalizability is low. Additionally, itemized summary statistics should be interpreted with caution, since our inclusion criteria was fairly broad, and because of the incompatibility of cross-study categorizations.

We included several studies with “multiple” vaccines because they were integration campaigns (i.e., integrating a new vaccine into an existent multi-vaccine program, or rolling out an intervention with multiple vaccines). This may lead to some cost inflation that would not have occurred were we to have limited our study pool to only those programs which administered one vaccine in isolation. However, we chose not to adopt such a restriction because 1) it would have reduced our sample significantly, ignoring otherwise useful information from multiple programs, and 2) it would have imposed a condition on costs which hypothetically might not even correspond to the rollout of an RTS,S campaign in the future (i.e., there is no reason to suggest at this point that RTS,S would not be rolled out in the framework of an “integrated” program).

Although some studies make a clear distinction between the cost of existing programs and the cost of introducing a new vaccine, most studies do not systematically separate capital costs and recurrent costs or average versus incremental costs. Very few studies make it clear how discounting of capital costs (including training costs as investments in human capital with an expected depreciation period of some years) has been handled. Capital cost is in general

annualized based on the life expectancy of equipment but with limited information.

The studies generally apply a provider or health care system perspective and few studies consider the wider societal perspective by, for example, taking into account the costs for families in terms of transport and opportunity costs such as time lost for other activities when accompanying their child for vaccination. However, the wider societal perspective is mostly relevant for a comprehensive evaluation of the economic value of vaccination and less relevant if the purpose of the assessment is more specifically to understand the cost structure to possibly improve efficiency and reduce costs.

Our aim was to support the design of a field study to estimate the cost of RTS,S rollout. Also by generalizing to vaccines as a whole, our results may be generalizable to vaccine campaigns at large, rather than just RTS,S.

A limitation of this review is that we used one database (PubMed) for our search, which may have limited the numbers of studies identified. There may be additional studies published in peer-reviewed journals, and it is likely there are numerous small specific studies in the gray literature that have been overlooked. Nevertheless, this review of 58 articles provides an indication of the likely cost estimates and potential budget required for introducing a new vaccine. To conclude, given the wide variation in the cost per dose (between and within countries) even in studies using consistent data collection tools and analysis methods across a large number of health care facilities in several countries, it would not be reasonable to try to fix a point estimate for the costs per dose. When considering inclusion of a new vaccine in countries targeted by this review, perhaps the overall interquartile range of US\$0.54 to US\$2.31 estimated here could serve as a reasonably precise baseline estimate but at the country level it would be useful to perform cost estimations strictly following the guidelines already available.

It would thus be commendable in future studies to adopt the method of the EPIC studies with a distinction between resource items (such as personnel, equipment, vehicles, buildings, etc.) and the various functions or activities each of these are used for. For example, personnel are participating in training, so the cost item is “personnel cost” but the actual activity is indeed “training.” In this review, we have observed that studies use inconsistent approaches with regard to reporting costs by item or by activity, making aggregation and comparison difficult. Combining cost items and activities in a matrix for cost calculation as proposed by Brenzel et al.⁵⁴ and illustrated in Figure 3 could greatly increase transparency and improve the understanding of the cost structure and

Line item	Activity						
	Routine facility-based vaccination	Record keeping and HMIS	Supervision	Outreach vaccination	Training	Social mobilization and advocacy	Surveillance
Salaried labor							
Volunteer labor							
Per diem & travel							
Vaccine							
Injection supplies							
Other supplies							
Transport/fuel							
Vehicle maintenance							
Energy costs for cold chain							
Printing							
Utilities communication							
Other recurrent							
Cold chain equipment							
Vehicles							
Lab equipment							
Other equipment							
Other capital							
Buildings							

Figure 3 Matrix of cost items and activities for structuring vaccination cost calculations.⁵⁴
 HMIS, Health management information system.

its determinants in order to increase efficiency and help planning resource requirements and financing needs. Additionally, aggregate studies such as this one would be of greater accuracy and applicability were the component costs categorized more consistently and transparently.

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Author contributions

All authors comply with the ICMJE criteria for authorship. J. Brew and C. Sauboin were involved in the conception and/or the design of the study. J. Brew and C. Sauboin participated in the collection or generation of the study data. J. Brew and C. Sauboin conducted the study. C. Sauboin contributed to the analysis tools. J. Brew and C. Sauboin were involved in the analyses and/or the interpretation of the data. All authors read and approved the present article.

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Supplemental Material

Supplementary material for this article is available on the *Medical Decision Making Policy & Practice* website at <http://journals.sagepub.com/home/mpp>.

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8. Study 5: Mapping the potential use of endectocide-treated cattle to reduce malaria transmission

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Mapping the potential use of endectocide-treated cattle to reduce malaria transmission

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Treating cattle with endectocide is a longstanding veterinary practice to reduce the load of endo and ectoparasites, but has the potential to be added to the malaria control and elimination toolbox, as it also kills malaria mosquitoes feeding on the animals. Here we used openly available data to map the areas of the African continent where high malaria prevalence in 2–10 year old children coincides with a high density of cattle and high density of the partly zoophilic malaria vector *Anopheles arabiensis*. That is, mapping the areas where treating cattle with endectocide would potentially have the greatest impact on reducing malaria transmission. In regions of Africa that are not dominated by rainforest nor desert, the map shows a scatter of areas in several countries where this intervention shows potential, including central and eastern sub-Saharan Africa. The savanna region underneath the Sahel in West Africa appears as the climatic block that would benefit to the largest extent from this intervention, encompassing several countries. West Africa currently presents the highest under-10 malaria prevalence and elimination within the next twenty years cannot be contemplated there with currently available interventions alone, making the use of endectocide treated cattle as a complementary intervention highly appealing.

Malaria control and elimination. Malaria continues to be one of the ten leading causes of death in low-income countries¹, with 92% of all new malaria cases in 2017 being confined to the WHO African Region². Six African countries (Nigeria, Democratic Republic of Congo, Burkina Faso, United Republic of Tanzania, Sierra Leone and Niger) accounted for almost half (49%) of all malaria deaths in 2017². Remarkable advances in the fight against malaria had been achieved between the years 2000–2015, yet these stalled in 2015³. Despite countries setting the ambitious goal of reducing malaria case incidence by 40% in 2020, relative to 2015, under the WHO Global Technical Strategy for malaria 2016–30⁴, the world is far from reaching the goal since no significant progress has been made in reducing global malaria cases in the 2015–2017 period². A number of challenges are hindering the attainment of this goal, including insufficient financing of malaria interventions, non-universal access to prevention and care, and the continued emergence of resistance to antimalarial medicines and insecticides². In all major malaria vectors, resistance to the four main classes of insecticide (pyrethroids, organochlorines, carbamates and organophosphates) is widespread across malaria endemic regions².

Vector control as the pillar intervention against malaria. Targeting the mosquito vector has been and will remain one of the pillars of malaria control, elimination and eradication efforts^{2,5}. The core vector control interventions (long-lasting insecticidal nets, or LLINs, and indoor residual spraying, or IRS) contributed to approximately 78% of the 663 million cases averted from 2000 to 2015⁶. These interventions have been highly effective as they reduce daily mosquito survival rates as well as rates of biting on humans, two parameters that drive onward malaria transmission⁷ due to their importance in determining vectorial capacity (the number

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of new infections induced by a given vector population)⁸. However, both LLINs and IRS interventions target anthropophagic, endophagic and endophilic mosquitoes, which are respectively vectors that are heavily reliant on human blood, feed predominantly indoors, and/or rest indoors⁹.

What LLINs and IRS interventions do not effectively address are mosquito behaviors that allow them to avoid contact with insecticides such as outdoor biting and resting, early exiting from houses after feeding, biting at dusk/dawn or at times when humans are not protected by nets and partial feeding upon livestock^{10,11}. These behaviors create advantageous temporal and spatial gaps for the mosquito which contribute to residual malaria transmission, defined as “Persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme”⁸. Controlling residual transmission requires new, complementary mosquito control strategies that go beyond the household walls^{12,13}. One notable problematic vector species in Africa is *Anopheles arabiensis*, which can exhibit all of these behaviors to some degree, in particular when choosing hosts for bloodmeals. *An. arabiensis* collected at different sites display vast variability (from 0% to 80%) in the proportion of bloodmeals obtained from humans versus other animals¹².

The role of livestock in malaria transmission. Livestock play an important role in the epidemiology of several of the most important diseases of man by acting as reservoirs for zoonotic pathogens (e.g. zoonotic tuberculosis, brucellosis, etc.) that can be transmitted to humans via direct contact, aerosol, ingestion, fomites, or vector. However, the role of livestock as a source of blood-meal for arthropod vectors of non-zoonotic human diseases has also been shown to influence epidemiologic patterns of human diseases, including malaria¹⁴.

Human *Plasmodium* parasites are not infectious to livestock, but zooprophylaxis has long been proposed as a complementary strategy to reduce malaria transmission¹⁵. This is achieved when infected mosquitoes are diverted to alternative blood-sources that constitute “dead-end” hosts and prevent the amplification of the parasite¹⁵. One important pitfall in the concept of zooprophylaxis is that although human *Plasmodium* parasites cannot infect livestock, when animals are kept close to humans they can increase malaria transmission by attracting increasing numbers of mosquitoes in a phenomenon known as zoopotentiality^{15,16}. Zoopotentiality has been shown to be exacerbated in areas with semi-intensive or semi-extensive cattle production, in which cattle graze freely during the day but sleep inside or in close proximity to human dwellings¹⁷. This type of production system is common practice in agro-pastoral and mixed crop livestock systems found throughout West Africa and in focal areas within East and Southern Africa¹⁸.

Although partially zoophilic vectors such as *An. arabiensis* feed upon animals and bite humans only occasionally and opportunistically¹², feeding upon animals is often coupled with other resilient behaviors such as outdoor biting and avoidance of insecticide treated indoor surfaces. These resilient behaviors allow mosquitoes to thrive in the presence of good LLIN and/or IRS coverage¹⁹ and thus enable residual malaria transmission¹¹. In many African countries, cattle are often dipped with insecticides to treat and prevent ectoparasites, a practice that has shown potential to control zoophagous vectors^{13,14,20} and thereby counteracting zoophagy-driven residual transmission. Dipping, however, has a relatively short duration against mosquitoes and is not free of safety issues caused by ingestion via licking. One attractive emerging alternative is the treatment of livestock with systemic insecticides or endectocides.

Endectocides. Endectocides are a type of systemic insecticide that have activity against both endo-parasites and ecto-parasites and are commonly used in veterinary medicine to improve livestock health and increase yield^{21–23}. Ecto-parasites force animals to expend a large amount of energy in defensive behavior, reducing feeding/grazing time, feed efficiency and milk production in the case of dairy cattle^{24–26}. Endo-parasites alter nutrient absorption, which leads to slower weight gain, reduced milk production and lower carcass quality²⁷. Among approved endectocides, the best-known classes are avermectins which include ivermectin, and several analogs such as moxidectin, selamectin and eprinomectin²³.

Ivermectin has been widely used by veterinarians for the control of parasites of livestock and companion animals for decades²⁸. It has low mammalian toxicity and is approved for human use²⁹. Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels in muscle and nerve cells of invertebrates, including malaria vectors³⁰. This binding causes an increase in the permeability of the cell membrane to chloride ions and results in hyperpolarization of the cell, leading to paralysis and death³¹.

There is an opportunity to manage residual malaria transmission driven by partly zoophagous vectors by administering endectocides, such as ivermectin, to livestock^{32–36}. Recent semi-field and field studies on *An. arabiensis* and *An. coluzzii* fed on ivermectin-treated cattle have found reduced survival, reduced blood meal digestion, reduced oviposition and reduced fecundity^{34,35,37}. Although all these studies show a significant impact on important mosquito life-history traits that should decrease the overall vectorial capacity, direct evidence that malaria prevalence is affected is lacking.

Livestock, malaria and endectocides, where to start? Malaria elimination may not be attainable with scale-up of IRS and/or LLINs alone in areas dominated by partly zoophilic vectors such as *An. arabiensis*. Instead, efforts could be complemented with vector control measures that address mosquito behavior leading to residual transmission, such as larval source management and systemic application of endectocides in humans or livestock^{35,38}. This review focuses on cattle given their large biomass, frequent rearing in rural communities and economic importance throughout Africa. Although coordinated mass-treatment of cattle might be logistically challenging, existing small-scale studies show significant impact on partly zoophilic vectors^{35,39}.

Given the potential added value of endectocide-treated cattle to reduce malaria transmission and the need for evidence-based priority-setting in order to optimize vector control, this study aims to identify the regions of Africa where a high malaria burden coincides with high cattle densities in the presence of a problematic vector with important feeding plasticity: *Anopheles arabiensis*.

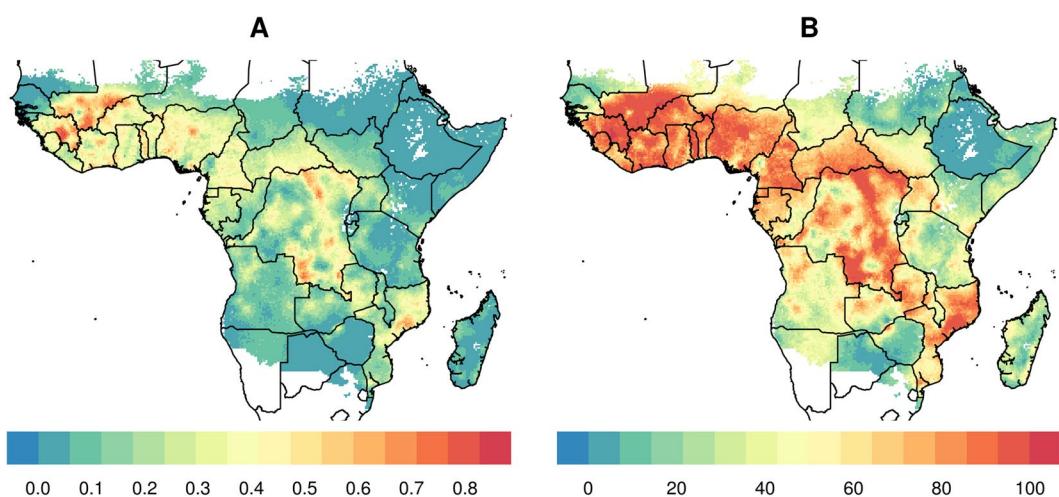


Figure 1. Plasmodium prevalence in 2–10 years old, using data aggregated and made public by the malaria Atlas Project (A) raw and (B) percentilized.

Methods

The raw data on cattle density per squared kilometer was obtained from the International Livestock Research Institute (ILRI), Food and Agriculture Organization of the United Nations (FAO) and the Université Libre de Bruxelles (ULB-LUBIES) (<https://livestock.geo-wiki.org/Application/index.php>). For *Plasmodium* parasite rate among 2–10 years old and the distribution of *Anopheles arabiensis*, data aggregated and made public by the Malaria Atlas Project was used (<https://map.ox.ac.uk/explorer/#explorer>) (downloaded October 2018).

The geographic attributes of the datasets (extents and projections) were standardized along with granularity to one surface using R (code at <https://github.com/joebrew/cowsquitoes>). The prevalence scale (0–1), the vector prevalence scale (0–0.847) and the cattle per square kilometer scale (0–infinite) were standardized to one 0–100 metric via percentilization (of Sub-Saharan African maximum).

Following standardization, the three percentilized metrics were combined by simple product. So, in the combined score, 0 means no *Plasmodium falciparum* among 2–10-year-olds, no *An. arabiensis* and no cattle, whereas 100 would theoretically mean the maximum (respective) values of the three. Anything between the two extremes represents some combination. This method assumes an equilinear value of percentilized *Plasmodium falciparum* parasite rate, *An. arabiensis* density and cattle density rate.

This combined score was calculated by country and first administrative division which were then ranked by median score and proportional area above the continent's mean.

Results

In Figs 1–5, maps of Africa are shown to investigate regions that could benefit to the largest extent from treating cattle with endectocide in order to reduce malaria transmission. As per Fig. 1, the greatest burden of malaria in Africa is observed in western and central Africa, as well as in regions of some southern African countries, including Mozambique, Malawi and Zambia. Figure 2 shows high cattle density in most non-deserted regions of Africa with the exception of large parts of some central African countries (Democratic Republic of Congo and Gabon), possibly due to the local dominance of rainforest, as well as large areas of Namibia, western South Africa and northern Mozambique. Presence and density of *An. arabiensis* are presented in Fig. 3. Noticeably, regions of high density overlap largely with regions of high cattle density (Figs 2B and 3B). In areas with high *An. Arabiensis* density (greater than the median pixel-specific value), the average percentilized cattle density is 70.1, compared with 58.2 in areas with no *An. Arabiensis* at all and 37.7 in areas with low (below median) *An. Arabiensis* density. By the same token, areas with high cattle density (greater than the median pixel-specific value), the average percentilized *An. Arabiensis* density is 51.2, relative to only 6.75 in areas with no cattle at all and 9.49 in areas with low (below median) cattle density.

In a similar fashion, there seems to be a relationship between parasite prevalence (Fig. 1) and cattle density (Fig. 2), albeit this relationship is less clean than the relationship between cattle and *An. arabiensis*. Areas with parasite presence have more cattle than non-parasite areas. In areas with high parasite density (greater than the median pixel-specific value), the average percentilized cattle density was 54.4, compared with 37.3 in areas with no parasites at all. That said, cattle density was highest (67.7) in areas with low (below median) parasite density. By the same token, areas which are dense in cattle have more parasite than non-cattled areas. For areas with high cattle density (greater than the median pixel-specific value), the average percentilized parasite density is 45.4, much higher than 28.7 in areas with no cattle, but slightly lower than the 58.8 in areas with low (below median) cattle density.

Figure 4 shows the index combining disease burden, cattle density and *An. arabiensis* density, thus indicating the locations with the highest potential of benefitting from treating cattle with endectocide. These areas are widespread in most sub-Saharan western African countries; somewhat present in Central African Republic, Kenya and Uganda; and punctual in Mozambique, Angola and Madagascar. Chad, South Sudan, Zambia, northern Namibia and southern Somalia display medium scores quite uniformly across the territory. In all other malaria-endemic

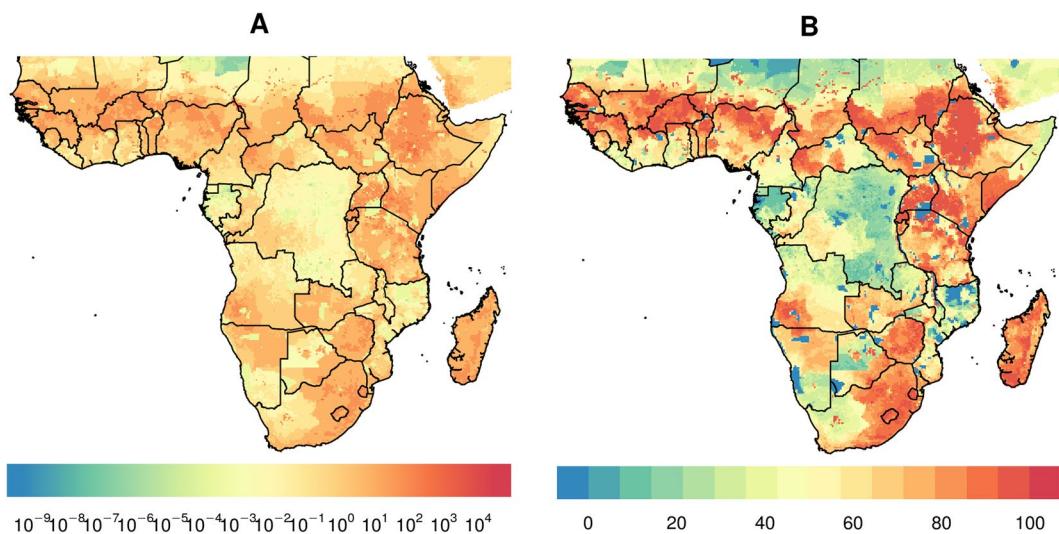


Figure 2. Cattle density per square kilometer (A) raw and (B) percentilized, obtained from the International Livestock Research Institute (ILRI), Food and Agriculture Organization of the United Nations (FAO) and the Université Libre de Bruxelles (ULB-LUBIES).

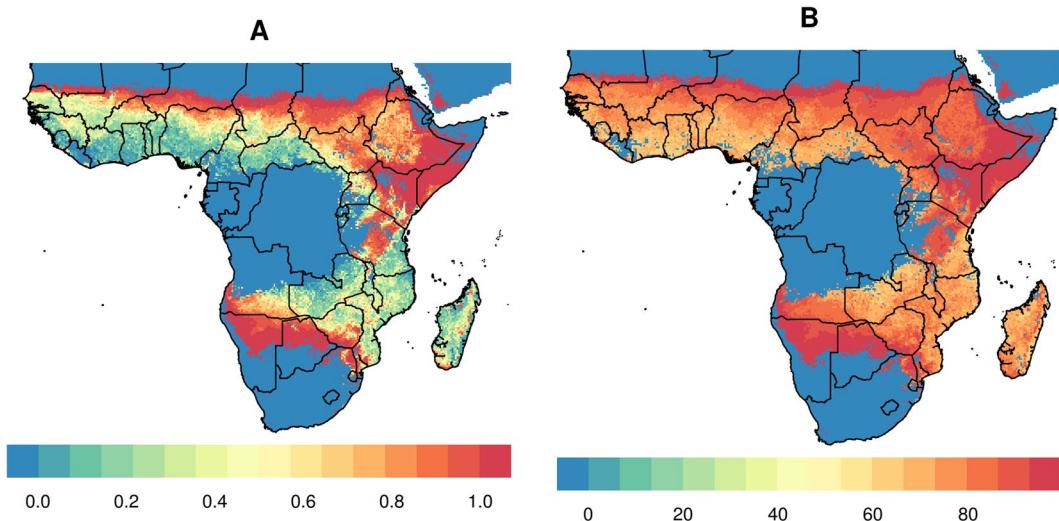


Figure 3. Density of *Anopheles arabiensis* (A) raw and (B) percentilized. Data aggregated and made public by the Malaria Atlas Project.

countries surfaces with low scores prevail, namely in Sudan, Djibouti, Eritrea, Ethiopia, Botswana, Malawi and central African countries, mostly attributable to the low local density of *An. arabiensis*.

When extrapolating overall surface results to the first administrative level, ranking them by suitability for endectocide-treated cattle according to their median score (Fig. 5A) and according to the percentage of unit area that is above the median continent score (Fig. 5B), the density of highlighted administrative units is most striking in a distinctive climatic block involving several regions of different countries: the savanna region underneath the Sahel in west Africa, where the potential for intervention is the greatest. There is, however, a scatter of administrative units highlighted as potential benefiters from the intervention in central and eastern sub-Saharan Africa, including parts of Somalia, Kenya, Uganda, Tanzania, Zambia, Malawi, Mozambique, Madagascar, Namibia and Angola. An interactive map with the individual components of the combined score in each first administrative division in Africa has been made available online at <http://www.databrew.cc/cow.html>.

Discussion

Controlling residual malaria transmission needs a comprehensive approach, integrating interventions that target the various mosquito behaviors¹¹ and using measures that go beyond personal protection¹². The specific portion of residual transmission that is driven by partly zoophilic vectors could be controlled with endectocides that reduce the lifespan of mosquitoes feeding upon cattle⁴⁰. This intervention appears to be a suitable vector control

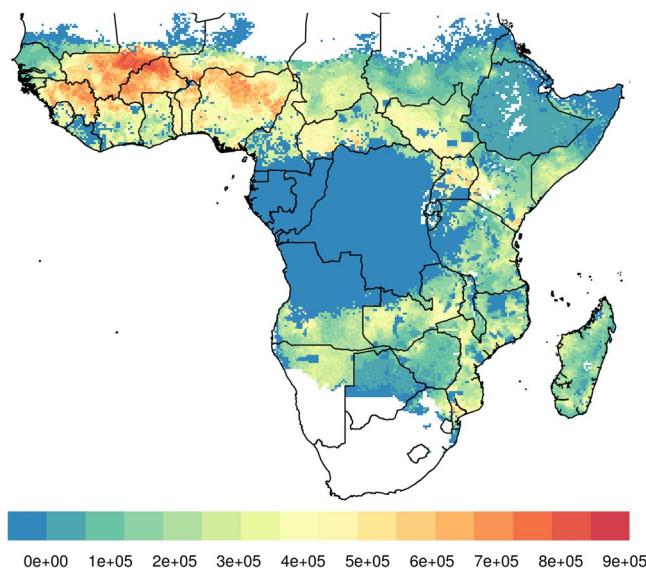


Figure 4. Mapping the results of the combined score obtained by combining the percentilized Plasmodium prevalence, and density of cattle and *Anopheles arabiensis*.

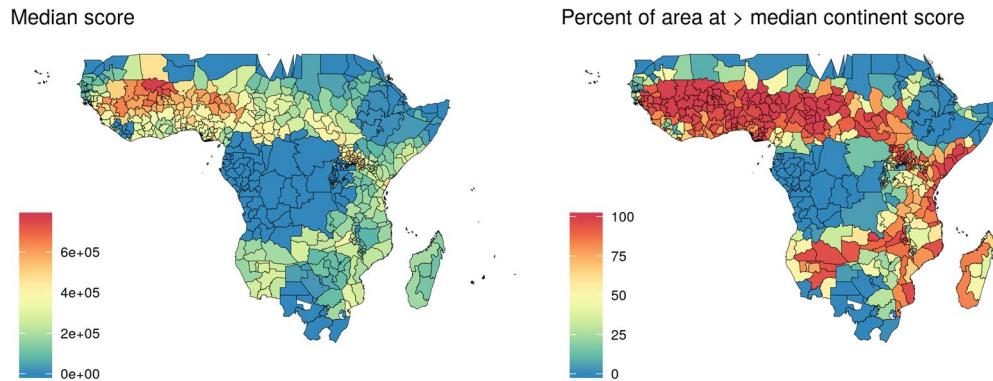


Figure 5. Mapping the combined score and ranking first administrative divisions by (A) median score in that unit and (B) divisions with part of their territory above the median continent score.

tool in vast areas of the African continent. This may be attributable to the fact that it targets *An. arabiensis* capitalizing on its partly zoophilic nature, together with other influencing factors. Recent evidence has identified *An. arabiensis* as the *Anopheles* species that is most widespread in the African continent⁴¹.

The analysis presented here identifies the African areas with theoretical higher potential to benefit from endectocide-treated cattle (ETC) as a complementary strategy for vector control. With no room for doubt, West Africa appears as the African region where ETC would be most effective. Not only does high under-10 malaria prevalence overlap with high cattle density, but it also coincides with the highest densities of the partly zoophagic *An. arabiensis* that currently sustain local residual transmission^{11,12}. In four west African countries (Burkina Faso, Guinea, Benin and Togo) all first level administrative units present median combined scores that are half of the maximum score or above (i.e., median score $\geq 50\%$). Burkina Faso has the administrative units with the highest median scores across Africa, together with the Sahel and Sudan regions of Mali. This makes these four countries highly eligible for country-wide ETC, and together with the named areas of Mali a region-wide strategy seems highly appropriate. Currently, West Africa is the region with the highest under-10 malaria prevalence and the only region in Africa where seasonal malaria chemoprevention (SMC) is part of the standard of care for children under five years of age. The addition of ETC may be one of the necessary ingredients for malaria control and eventual elimination in a region where the latter possibility cannot be contemplated with currently available interventions alone.

Previous modelling studies have estimated that using a combination of currently existing interventions (LLINs, IRS and three rounds of mass drug administration, or MDA) pre-elimination levels would only be achievable in 26 (95% CI 22–29) of 41 African countries within the next 20 years⁴². In the remaining 15 countries, additional new interventions will be necessary to achieve pre-elimination levels. In Fig. 5, our analysis sheds light on the countries with administrative units that have the greatest potential of benefiting from ETC (median

score $\geq 50\%$). All the countries highlighted in our study, with the exception of Sierra Leone and Guinea, are amongst those remaining 15 countries where previous models have predicted that no combinations of the other key malaria interventions would make it possible to achieve pre-elimination in the next 20 years⁴². Therefore, ETC could become a positive contribution to the malaria toolbox in many regions of Africa, and especially in regions of those countries where new interventions are most needed. Testing the effectiveness of ETC in combination with other strategies seems particularly relevant in the administrative units highlighted in these 13 countries.

Although country-wide ETC is predicted to be useful across an entire country in only a few examples (Fig. 5), its potential in certain administrative units is certainly worthy of exploration. Targeting malaria interventions at the local level has the potential to maximize impact and cost-effectiveness. For example, a recent study evaluating the cost-effectiveness of combinations of different malaria interventions (insecticide treated nets, IRS, MDA and SMC) across Africa estimates 32.1% (95% CI 29.6–34.5) cost savings when adopting policies at the provincial level compared to country-wide policies⁴². On the other hand, the potential for a region-wide intervention (i.e., the savannah region underneath the Sahel in West Africa) (Fig. 5) may provide the opportunity for leveraging economies of scale and transfer of knowledge and skills across countries to address the pressing issue of malaria control in West Africa and beyond.

Interestingly, upon observing the highly overlapping distributions of cattle and of *An. arabiensis* one is compelled to suspect a certain level of coevolution, more so given the zoophagic nature of the vector. Evidence of the coevolution of other members of the *Anopheles* complex, namely *An. gambiae* and its vertebrate host for bloodmeals (humans), has been previously observed and reviewed by Cohuet *et al.*⁴³, reflecting the plasticity of the vector's genetics and its genetic capacity to specialize to the human host and its environment. On the other hand, their co-existence could be coincidental or dependent upon factors such as requiring similar living conditions: both cattle and *An. arabiensis* may not thrive in deserted nor rainforest regions, which are almost the only areas of Africa where neither of them are densely present. Cattle go where people go. However, the presence of *An. funestus* and *An. gambiae* in the central African rainforest indicates the viability of the *Anopheles* mosquito in such environments.

Similarly, areas of higher malaria prevalence may also have a tendency towards higher cattle densities, albeit the overlap is less strict than in the case of *An. arabiensis* with cattle. This observation provides support for a zoopotential effect in some areas, where the presence of cattle as an alternative mosquito feeding source may be attracting an increasing number of mosquitoes towards human populations if they live close to cattle. In some regions and/or households, cattle are kept outdoors and away from the home hence posing no major risk of zoopotential, while in other regions cattle are kept indoors or in close proximity to humans due to security reasons. Although speculative at this point, the observation warrants further investigation, as documented zoopotential would further support ETC implementation, particularly in areas where cattle ownership and nocturnal husbandry close to the household are more frequent. Interestingly, the most cattle-dense areas are those with high parasite prevalence but not those with the highest parasite prevalence, and the most parasite-dense areas are those with some cattle but not those with most cattle. This observation may provide a hint towards further investigations on the effect of different husbandry practices, the vectors present in those areas, on a potential relationship between cattle and parasites by which both may thrive within a certain equilibrium between the species, or on any other potentially influencing factors.

For this exercise, the currently most complete and updated publicly available data were used. The three datasets used employ measurements at sub-country levels to model continent-wide estimates at quite granular levels of spatial resolution. A variety of data sources are inputted for the creation of those three models, and the accuracy of the original models in different regions depends on the nature, quality and granularity of data collected. Malaria prevalence and *Anopheles* data are based on an extensive database containing over 40,000 geo-referenced cluster locations' parasite rate survey records⁴⁴, and are therefore the probably most reliable models of the three. Most data used to produce the models are more recent than 2000^{45–47}. Given that for each raster surface, the data inputted in our models is not field data but modelled data, the parameters obtained are also somewhat speculative. To this extent, the maps presented here should be understood as the first step towards obtaining more insight on the areas where it is most relevant to conduct more targeted investigations (including obtaining field data on malaria prevalence, cattle density and *An. Arabiensis* density) and test ETC in different contexts.

Amongst the limitations of this current work stands the lack of data on the proportion of the malaria prevalence that is attributable to transmission via each mosquito species in each surface. This limits the ability to infer whether ETC, an intervention targeting only mosquitoes that display plasticity in the species they feed upon, would be able to avert most malaria transmission or only a small part of it in areas presenting a wealth of mosquito species. The same applies to the lack of granular data on mosquito behaviors and other factors that potentially affect the effectiveness of the intervention, including differing vectorial capacities of the same mosquito species across Africa⁴³ and the diversity of cattle ownership and husbandry practices that determine proximity of cattle to humans.

Recognizing these limitations, the maps we have generated employ percentilization of the parameters imputed to show the relative potential for an ETC intervention compared to the rest of areas in Africa. Therefore, we have effectively identified ideal locations where details on vector contribution to proportion of disease transmission, mosquito feeding behaviors and cattle husbandry practices should be investigated to further improve our understanding of where ETC may be most effective.

If ETC was proven effective for reducing malaria, other gaps in knowledge would need to be addressed. Some examples include evaluation of ETC cost effectiveness in combination with other strategies, assessing the intervals of reapplication of endectocides to ensure lengthy efficacy, assessing the best preemptive approach to resistance (mosaic, rotation, refugia or alternation) through operational research and finally evaluating the attitudes and perception of cattle owners to the proposed strategy, particularly if human ivermectin is being piloted or deployed in the same areas.

It is particularly important to consider the cattle owners' perception of ETC, as endectocides have long been used for control of both ecto- and endo-parasites that reduce productivity (e.g., low efficiency of feed conversion, weight gain and milk production) and cause economic losses^{21,22,48}. Treatment of livestock with endectocides has also been successful against *Tse tse* flies in sub-Saharan Africa⁴⁹, tick-borne diseases worldwide, and a variety of other biting and/or nuisance insects including flies, biting midges, mites and lice²². At approved labeled doses, topically or systemically applied endectocides provide the sufficient and/or sustained dosage required for reduction of mosquito survival rate below elimination threshold^{50,51}. Consequently, by employing endectocides for malaria control, cattle owners will also enjoy direct and indirect benefits such as enhanced milk production, reduced burden of parasites and healthier animals⁵².

Being able to capture the potential direct and indirect benefits associated with ETC would be critical in any cost effectiveness analysis of the intervention. In addition to the potential economic gains achieved from improved livestock productivity, healthier livestock have a profound positive effect on human nutrition and health, especially in poor communities highly reliant on livestock⁵³. Livestock parasites contribute to human malnutrition by affecting both the food available to human populations and the income generated by populations dependent on livestock production. These two factors in turn contribute to poverty and a weaker physical state, making populations more vulnerable to disease and malnutrition, and less able to obtain protection. Recent mathematical modelling suggests that non-zoonotic livestock disease can ultimately have a more significant impact on human health than human disease alone⁵³, making the treatment of livestock with endectocides very appealing.

In conclusion, killing competent mosquito vectors of malaria when they feed upon animals by treating livestock with endectocides may be critical for tackling residual transmission driven by zoophagic and opportunistic mosquitoes⁴⁰. Through this study, we have identified those geographical areas where using an ETC intervention would be most likely to prove effective at reducing cases of malaria, and where we should focus our research efforts going forward. As an additional, and perhaps not insignificant benefit, ETC has the potential to improve the overall health and nutrition of human populations through its impact on livestock health. Furthermore, because endectocides' mode of action differs from that of pyrethroids, they provide a novel complementary intervention to LLINs and IRS. In essence, employing ETC interventions could reduce the burden of insecticide resistance and prolong the effectiveness of other insecticide-based interventions. This is most necessary in the context of addressing *An. arabiensis*, the main vector targeted through this intervention, as it is the only *Anopheles* species that has been reported to display resistance to the four main types of insecticide⁴¹. Should ETC become a new intervention in the toolbox for malaria control and elimination, the current analysis shows that those areas where it has the potential to be most effective are also those that most need it, where elimination is not within reach with the currently available interventions – perhaps not coincidentally.

Data Availability

All datasets are publicly available from the cited sources. All code is available at <https://github.com/joebrew/cowsquitoes>. The interactive online map is publicly available at <http://www.databrew.cc/cow.html>.

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9. Study 6: Is malaria control profitable? Return on investment of residential fumigation at a sugarcane processing facility

Is malaria control profitable? Return on investment of residential fumigation at a sugarcane processing facility

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1. Introduction

Malaria accounts for a half million annual deaths worldwide (Ashley et al., 2018; White et al., 2014; World Health Organization, 2019). Though rapid improvements in technology and funding have led to important reductions in malaria's global burden, the scale-up in activities required for elimination will mean new partnerships and actors. One promising potential stakeholder in global malaria eradication is the private sector, given its omnipresence and potential to benefit directly from the elimination of malaria. But little evidence exists demonstrating how private sector entities can engage with malaria control and benefit at the firm level.

The evidence of malaria's negative effects on health and wealth are amply described in the public health and economics literature. However, very little exists in the literature examining the costs and benefits of malaria control from a private ledger perspective (ie, the point of view of a business investor). Unlike a government or individual, a private firm investing in malaria control may be most interested not in its long-term macroeconomic effects, nor its short-term personal health effects, but rather on the impact on productivity (and the extent to which that productivity benefits accrue to the firm), absenteeism, and the opportunity costs of expenditures in malaria control. Importantly, since private firms do not capture (in terms of financial benefit) many of the positive externalities of a reduction in malaria, much of the existing literature on the economic benefits of malaria control are not applicable. In other words, though the benefits of malaria control are large (exceeding costs by a

factor of up to 20 (Jamison et al., 2015)) and well known, the portion of those benefits accrued by a private firm investing in malaria control is unknown.

To address the question of the profitability of malaria control activities from the standpoint of a private firm, we analyze administrative data during a 4 year period from a private sugar facility in Southern Mozambique. We use absenteeism, which is directly correlated with the productivity losses associated with malaria infection, as our outcome of interest. We assess the effect of preventive malaria technology - in the form of indoor residual spraying (IRS) - on absenteeism, and demonstrate that the firm's engagement in malaria control not only improved worker health, but also generated positive economic returns for the firm.

Since a worker's likelihood of absence is moderated not only by whether his/her home has been fumigated (ie, treated with IRS), but also by the time since fumigation as well as the fumigation status and proximity of neighbors' homes, we employed a time-discounted "community protection" concept in which an individual's protection status is the distance-weighted average of all nearby households' protection status, weighted by proximity to the individual in question and declining quasi-linearly over the course of the effectiveness period of IRS (approximately 12 months). We regress absence against this "community protection" score, adjusting for both individual fixed effects as well as the lagged precipitation. Having estimated the effect of community protection on absence, we then run a series of scenario simulations to generate hypothetical community protection scores with different fumigation strategies, and convert the estimated absence rates, as well as associated program costs, into returns on investment.

We find that the firm's indoor residual spraying program is associated with a 3.7 percentage point reduction in absenteeism from 13.0% to 9.3%. This reduction is concentrated primarily among permanent workers who both benefit more significantly from IRS' absenteeism-reducing effect and make up a larger share of the workforce in terms of days worked. We estimate that the savings from reduced absenteeism outweigh the costs, with a program-wide return on investment of 100%, assuming daily wages of temporary workers to be approximately \$7 and permanent workers to be approximately \$10. Our analysis is intentionally restrictive, excluding any long-term or secondary benefits accrued from the improved health status of workers. Our scenario comparison suggests that this figure could be optimized, but is already near the top-end of its potential. We attribute the observed program optimization to the fact that the program already incorporates a relatively large degree of flexibility in its fumigation operations (ie, an area may be prioritized for fumigation if residents complain of mosquitoes, or if multiple residents fall ill with malaria). The lack of a fixed structure to program operations appears not to be a program flaw, but rather the reflection of flexible responsiveness to constantly-changing entomological and epidemiological realities.

This study does not endeavor to expand the current body of knowledge regarding malaria's ill effects on individuals and societies; rather, it aims to provide empirical evidence pertaining to a facet of malaria economics with very little in the literature: malaria control from a private-sector investment perspective. Our study adds to the existing literature by showing the effect of specific malaria control interventions on worker absenteeism, and translating that effect into a return on investment. Unlike in previous studies on the effectiveness of malaria control interventions (which

generally find a positive effect, albeit subject to potential ecological bias, and analyzed at the level of society rather than the firm), we focus solely on one firm carrying out one intervention, taking advantage of individual-level data, and analyze results from a ledger perspective.

This paper is organized as follows. [Section 2](#) describes the background on malaria, its economic burden, the role of the private sector in its control, specifically in Mozambique and at the firm itself. [Section 3](#) describes the data we collected, variables of interest, our identification strategy for estimating the program's effect, and the conceptual challenges to modeling interventions with a high-degree of "spillover". [Section 4](#) gives an overview of results and counterfactual scenarios, and [Section 5](#) concludes.

2. Background and setting

Malaria's economic burden and prevention

Malaria has a large economic impact. At both the individual (Cole and Neumayer, 2006) and collective (McCarthy et al., 2000) levels, it affects behavior related to saving and investment. In the short-term, malaria reduces one's ability to work and imposes a financial burden both on oneself as well as caretakers (Ajani and Ashagidigbi, 2010; Asenso-Okyere and Dzator, 1997), and affects risk perception, productivity, absenteeism (Nonvignon et al., 2016), human capital accumulation (Castel-Branco, 2014), mortality, and costs of care (Sachs and Malaney, 2002).

There is ample economic literature on malaria's negative effect on gross domestic product (GDP and growth (Hong, 2011; McCarthy et al., 2000; Orem et al., 2012; Sachs and Malaney, 2002). Historical quasi-experimental studies have shown that malaria elimination leads to immediate improvements in under-five mortality, as well as increases in average years of schooling and the likelihood of employment later in life (Barofsky et al., 2015). Successful elimination campaigns in diverse settings have been shown, via quasi-experimental studies, to significantly improve lifetime female educational attainment (Lucas, 2010). The gains from malaria elimination go beyond education. While Barofsky showed immediate improvements in males' ability to find wage work following an elimination campaign, Bleakley showed long-term gains in adult labor productivity and income as a result of decreased exposure to childhood malaria (Bleakley, 2010). This is in line with Cutler's study on malaria elimination in India, which showed significant gains in household consumption following a 1950s elimination campaign (Cutler et al., 2010). Though Cutler did not find the educational gains common to most elimination studies, studies with more granular data on education, such as Thuilliez's 2010 longitudinal analysis of Malian schoolchildren, suggest that malaria reductions lead to decreased absences, and improved educational outcomes (Thuilliez et al., 2010).

These studies make a strong case for malaria's high economic costs and the corresponding benefits of its elimination or reduction. But they focus on these benefits from a purely *societal* perspective; that is, they strive to quantify the gains in both health and wealth to society itself, rather than to the hypothetical funder of the intervention. They find that the benefits likely outweigh the costs of the intervention, but this should come as no surprise since (a) malaria control and elimination

initiatives are relatively affordable at scale and (b) the public welfare perspective allows for the incorporation of long-term, aggregate-level benefits in education and the economy, even though these benefits are disperse and relatively small at the individual-level. Even more recent studies on targeted campaigns generally look at societal-level benefits in the form of disability-adjusted life years (DALYs), days of lost productivity, etc. (Howard et al., 2017). These studies, unanimous in their conclusions that malaria's elimination has large non-health benefits, do not differentiate between the direct beneficiaries (such as the recipient of a household-level malaria control intervention) and those who indirectly benefit through positive externalities (their neighbor), nor do they take on an investment perspective (other than that of the "investor" as society itself).

The role of the private sector in malaria control

From the perspective of the private sector, however, investing in malaria control is not so clear-cut, since the benefits are often disperse, long-term, and difficult to quantify. Public health interventions targeting malaria - and their corresponding cost-effectiveness evaluations - most often focus on impacts pertaining to public welfare, such as an increase in life years adjusted for disability or quality (Gunda et al., 2016; Gunda and Chimbari, 2017; Hanson, 2004). Though population-level health is certainly of importance to businesses, and improvements in health incidentally improve the economy at all levels (Vecchi et al., 2013), these improvements may be too dispersed or long-term to incentivize private sector involvement in health campaigns. In other words, the returns for malaria control are

less for the private sector because (i) they capture only part of the benefits and (ii) the private sector does not benefit from the positive externalities.

Just as the benefits of malaria control to the private sector are more limited than those to the country as a whole, considerations regarding costs for a firm are also distinct than those for a government. Though many firms in endemic regions engage in malaria control programs, this should not be considered, *per se*, evidence of its cost-effectiveness (since the extent to which corporate social responsibility plays a role is unknown) (Joe Brew Celine Aerts, n.d.).

The literature on private sector malaria control

In general, large firms operating in malaria endemic regions consider malaria to be an important enough issue to merit at least some investment (Pluess et al., 2009).

Several studies examine the effect of foreign firms engaging in large-scale malaria control campaigns (Han, 2015; Kaula et al., 2017). AngloGold-Ashanti, in partnership with local and national government in Ghana, invested in a well-rounded malaria control program in 2005, and saw worker absenteeism fall by 50% in 13 months (Ccm, 2016). Lafarge's simultaneous investment in a comprehensive malaria control program in Benin was associated with an average 41% reduction in absenteeism among workers over the course of 4 years (Ccm, 2016; Egedeye et al., 2011).

Zambia Sugar Plc, Zambia's largest sugar processing facility, saw annual malaria cases at its company clinic fall from nearly 3,000 in 2001 to less than 500 by 2005, following investment in a malaria control program. Marathon Oil's investment of 15 million US in vector control, education, net distribution and malaria treatment on Bioko Island in Equatorial Guinea lead to an estimated 95% reduction in the number

of parasite-infected mosquitoes and 50% reduction in malaria incidence among young children (Asquino, 2016; Overgaard et al., 2012). A PATH study in Zambia found a return on investment of 28% among three companies investing in employer-based malaria control (Mouzin and Al., 2011).

Though certainly suggestive of high returns on malaria control investments, these studies generally consider population health as the outcome measure of interest, rather than worker absenteeism or productivity. They are also mainly trend analyses, lacking well-defined causal identification strategies. Similarly, they often neglect to differentiate between those clinical costs which are absorbed by the local health system versus those which are absorbed by the firm itself. When absenteeism itself is considered, the apparent effects of malaria control have generally been found to be high, but causation is difficult to establish, given that the previous studies rely on aggregate data.

Importantly, two previous studies do utilize worker-level data to estimate the effect of malaria control on productivity. A World Bank analysis of Nigerian sugarcane cutters found that the simple availability of testing and treatment increased productivity by 10% in the weeks following the provision of services, the conclusion being that both the treatment and the test result were effective in increasing productivity, the latter simply increasing the information available which could influence personal labor allocation decisions (Dillon et al., 2014). A randomized controlled trial (RCT) in Zambia showed an even greater effect from investments in preventing malaria, using individual-level data: farmers given bed nets saw fewer days lost to illness (both directly and due to caretaking responsibilities for ill family members), translating to

an increase of approximately 15% in crop yield(Fink and Masiye, 2015). Though compelling, the Nigerian program only dealt with medical services (diagnostics and medication), rather than preventive interventions, and the Zambian RCT examined individual farmers, rather than estimating benefits to a firm.

A multitude of studies have examined the effects of other diseases, such as HIV/AIDS, on productivity and wealth (International Labour Organization, 2002; Ruger, 2004; Ruger et al., 2012; Sendi et al., 2004; Stillwaggon, 2005). There have also been numerous analyses of the feedback loop between wealth and health in developing countries (Asenso-Okyere et al., 2011; Devkota and Upadhyay, 2013; Farrell, 2006; Hussain and Perera, 2004; Kirigia and Muthuri, 2016; Laxminarayan, 2007). In general, infectious disease is associated with significant reductions in productivity, whereas initiation of treatment has the opposite effect (Thirumurthy et al., 2005). Though relevant, these studies generally look at diseases with a longer-term natural history, do not take into account prevention or treatment costs, and take on the perspective of the public sector (as opposed to a private investor), accordingly considering as "benefits" in the cost-benefit equation many effects which accrue outside of the strict realm of the private actor.

In the literature, making the "investment case" for malaria control or elimination generally implies that the investor is the public sector, and takes into account those costs and benefits which are applicable from a public welfare point of view (Shretta et al., 2017). For example, an economic analysis by the Corporate Alliance on Malaria in Africa on the Bioko Island Malaria Control Program found a 4:1 cost-benefit ratio, but the perspective in this case was considered to be the

“community” (Egedeye et al., 2011). Though appropriate in most cases to consider benefits accrued to the community (the government or institutions interested in public welfare primarily being the primary malaria control agents in most locations), the findings of these studies are rarely applicable to the private sector, and even less so at granular levels (such as an individual firm). In the case of a private firm not engaged in “corporate social responsibility”, it is not clear whether investing in malaria control would be profitable or not. This lack of clarity not only may discourage private investment in malaria control, but also makes it difficult for governments to pinpoint the correct amount of subsidy (if applicable, such as in the case of a government wanting to incentivize large firms to take care of their workers’ health by offsetting part of the cost of doing so) to encourage private sector scale-up in malaria control (Alonso et al., 2017).

The literature on the effect of sugarcane cultivation on malaria risk is mixed. While some studies have found that the prevalence of malaria vectors in sugarcane areas to be similar to that of uncultivated areas (and less than in areas dedicated to other forms of more water-intensive agriculture, such as rice) (Ijumba et al., 2002), other studies have found significant increases in factors associated with malaria transmission at large-scale sugarcane facilities relative to traditional, small-scale farming and non-irrigated farming (Jaleta et al., 2013). Regardless of the effect the presence of a sugarcane farm *per se* on local malaria epidemiology, the time spent outdoors by sugarcane workers, the fact that many workers are migrants, the socioeconomic status of manual laborers, and their sometimes precarious housing situations, all suggest that sugarcane farmers are likely at increased risk of malaria infection (O’Laughlin, 2016). This is important, given that even among occupations

with far less inherent exposure to mosquitoes (such as health professionals), malaria is one of the primary causes of work absenteeism in malaria-endemic countries (Burton et al., 1999). There is also some concern regarding the effect of large-scale insecticide use - common at essentially all Sub-Saharan African sugarcane farms - on insecticide resistance among mosquitoes in the area. A study in Belize found that mosquito populations on the edge of sugarcane fields had higher tolerance to insecticide than similar populations in the core of fields or outside of the periphery (Dusfour et al., 2009). Sugarcane areas may offer the standing water necessary for mosquito breeding, but also perhaps attract mosquitoes which would otherwise be elsewhere, due to compounds in sugarcane pollen (Wondwosen et al., 2018).

Malaria in Mozambique

100% of the Mozambican population are at risk of malaria, living in what the WHO classifies as a “high transmission” area (Moonasar et al., 2016; World Health Organization, 2019). Annually, Mozambique has more than 8 million clinical malaria cases (an annual incidence of approximately 300 per 1,000 residents), with an estimated 14,000 deaths. Malaria accounts for 29% of all deaths, and 42% of deaths among those under five years of age (INE, 2011). Since 2013, Mozambique has seen a gradual increase in the incidence of malaria (Moonasar et al., 2016). 100% of the malaria in Mozambique is of the *Plasmodium falciparum* species, with *Anopheles funestus*, *gambiae*, and *arabiensis* as the primary mosquito vectors of the disease (WHO, 2015).

Poverty is rife in southern Mozambique, and its associated illnesses take their toll on the population. The community prevalence of HIV/AIDS is as high as 40% (González

et al., 2012); even in a more recent study suggesting a much lower prevalence of 22%, the risk of infection is still twice that of nearby areas (Mocumbi et al., 2017). Recent years have seen a three-fold increase in tuberculosis (García-Basteiro et al., 2017). Malaria, which has the greatest mortality burden due to the fact that the young are especially vulnerable to its effects, is perennial, though worse during the rainy season (December - March) (Saúte et al., 2003). Adult malaria prevalence is very high, albeit much of it asymptomatic (Mayor et al., 2007). In regards to worker health, malaria is Maragra's primary concern, being so important as to justify the existence of both an on-site testing laboratory and clinic, as well as a malaria control department.

A significant sector of the economy in Mozambique is dominated by large-scale foreign direct investment projects (Castel-Branco, 2014; Robbins and Perkins, 2012), and the role of the private sector in health generally, and malaria specifically, is unequivocally important. Large agriculture and extractive industry firms take up wide swaths of land and employ hundreds of thousands (German et al., 2013). The Mozambican state has encouraged large-scale enterprise with the aim of general economic development (Buur et al., 2012). And where large firms exist, they often take on social roles such as housing and health care (Buur et al., 2012; Winkler, 2013). At times, this role is necessary from a purely practical standpoint; in other cases, it is employed under the auspices of "corporate social responsibility" (Azemar and Desbordes, 2009; Curtis et al., 2003). Regardless of the language used, it is clear that private industry plays an important role in public health in Mozambique (Castel-Branco, 2014; Robbins and Perkins, 2012).

Study area

Sugar has been systematically cultivated in Mozambique since the late 1800s. The Incomati Estates company, a small sugarcane processing facility started by a Scotsman on the banks of the Incomati River in 1913, was the first firm to export sugar from Mozambique. Following its purchase by international investors in the 1950s, it (along with the rest of the industry) expanded significantly, exporting to both Europe and the United States. In the late 1960s, a Portuguese family opened the Maragra Açúcar company, while a group of foreign investors started the nearby Marracuene Agrícola Açucareira mill. By the early 1970s, sugar grew to account for greater than 10% of Mozambique's national exports. Nationalized following independence in 1977, the industry's production levels fell from 320,000 annual tons to fewer than 15,000 by 1992. After the end of the civil war, foreign investment revived the sugar industry, and by 2011 production had surpassed its 1972 peak.

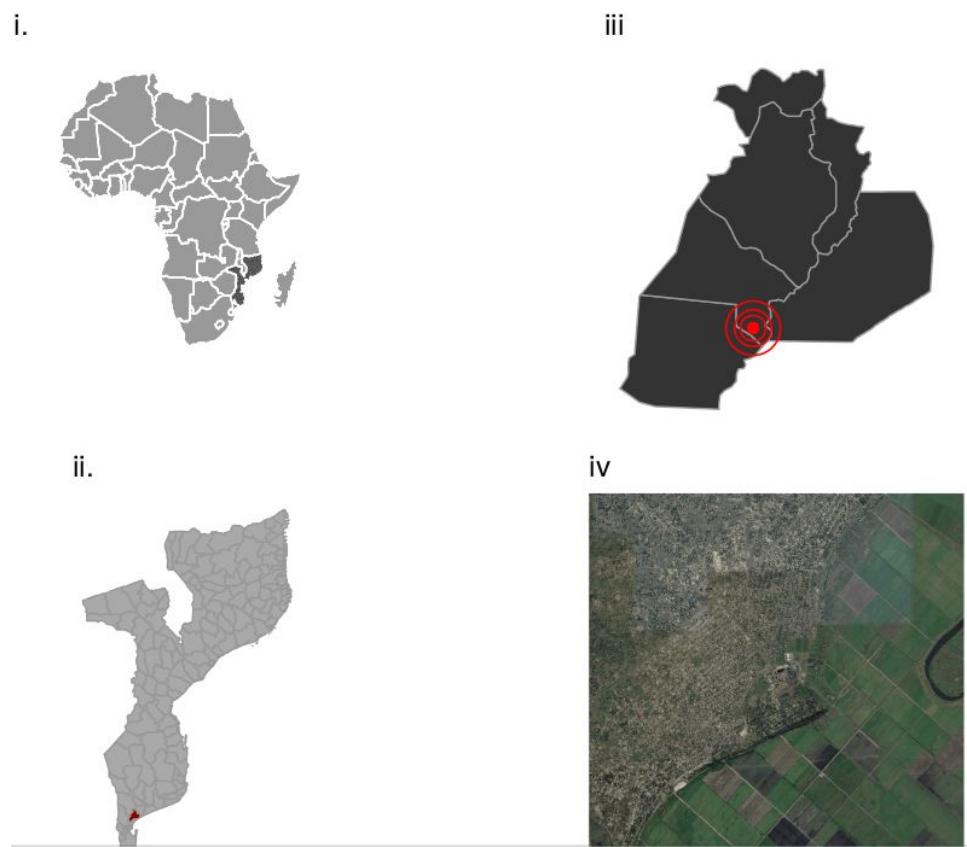


Figure 1. (i) Mozambique in Africa, (ii) Districts of Mozambique with Manhiça highlighted in red, (iii) District of Manhiça with Maragra highlighted in red, (iv) Maragra SA with surrounding fields and village

The mill of the Maragra Açucar SA (a subsidiary of the Illovo sugar company, henceforth referred to as “Maragra”) was nationalized in the 1970s (like all other Mozambican mills), went through a period of low production, and then fell completely out of use by 1984. It re-opened in private hands in 1992, and was renovated by a group of international investors in 1998. Today, Maragra accounts for roughly one quarter of Mozambique’s overall sugar production (second only to the nearby Xinavane mill run by the Hulett Sugar Tongaat company) (Sutton, J., Mapa empresarial de moçambique). With a favorably close location to the port of Maputo, ample land (approximately 90 square kilometers of plantation, and 5 squared

kilometers of factory grounds), approximately 5,000 employees (of which three quarters are seasonal), and a mill with the capacity to process not only all the sugarcane grown on Maragra's land, but also the cane of the many nearby smallholders (O'Laughlin, 2016), Maragra has so far been able to weather the 2016 Mozambican crisis and concurrent collapse in global sugar prices.

Maragra (figure 1, panel iii) is located in the district of Manhiça (figure 1, panel ii), a semi-rural area in the south of Mozambique (figure 1, panel i). 80 kilometers north of the Mozambican capital of Maputo, the district is low-lying, consisting largely of savannah and wetlands along the Incomati River. Most of the area's 160,000 residents (Sacoor et al., 2013) work as subsistence farmers. Migration from the area to South Africa for the purpose of employment in the profitable construction industry is common, especially among men (Nhacolo et al., 2006), as is migration to the area (from other parts of Mozambique) for seasonal work on the sugarcane plantations at Maragra and the slightly larger facility in Xinavane (at the district's border with Magude) (O'Laughlin, 2016).

Maragra workers are mostly seasonal, working for the firm approximately half of the year during harvest time, and cultivating crops, working in construction, or going unemployed (or working elsewhere) during the other half. Though many workers live "on-site" (ie, within the delineated property of the firm itself), a sizable minority resides in the environs (figure 1, panel iv). For workers living on-site and their co-residing family members, Maragra provides indoor residual spraying (IRS) using ACT (alpha-cypermethrin) and DDT (Dichlorodiphenyltrichloroethane), the former being applied preferentially to areas closer to the fields.

3. Materials and methods

Data collection

In collaboration with the sugar processing facility, we collected administrative data for the four year period from January 2013 through December 2016. Data came from four sources: (i) the Human Resources' roster of worker details and absences, (ii) the facility's on-site clinic's medical and laboratory records, (iii) the facility's on-site malaria control program's records pertaining to the dates, chemicals, and location of IRS activities, and (iv) interviews with company employees pertaining to costs, data limitations, etc. Digitization and collection of data took place during the period from March 2016 through May 2017. Supplementary data pertaining to worker characteristics was obtained from the Centro de Investigação em Saúde de Manhiça's (CISM) demographic census, which covered workers from the district, but not those who recently migrated from other parts of the country (Nhacolo et al., 2006).

There is no publicly available weather station data specific to Manhiça district or the Maragra facility. Therefore, we retrieved weather data for all Mozambican stations from NOAA and estimated daily precipitation at the centroid of Manhiça using a simple interpolation method whereby the district's weather conditions were estimated to be a function of all Mozambican weather stations' reported conditions, inversely weighted by kilometers from district centroid.

Maragra regularly employs IRS at on-site worker households in order to reduce those workers' (and their families') risk of malaria infection. IRS works both by killing

the malaria vector (mosquito) and deterring it from approach, thereby preventing infection of the household occupants (Oxborough et al., 2019). When administered correctly, IRS is a low-risk intervention to its recipients, and is assumed not to affect absenteeism in the short-term (to the extent that it may cause negative side-effects, these are generally long-term) (Eskenazi et al., 2019; Murray et al., 2018). It is preventive only, and does not cure current malaria infection, nor does it affect the parasite load of living mosquitoes. Workers living off-site (our control group) also may have received IRS at some point during the study period (from government programs). Even though we do not have reliable person-level data on IRS carried out by the government, off-site workers are a suitable control in the sense that they represent “business as usual” (ie, what would happen if the company carried out no IRS and relied solely on public interventions). Using company HR and clinical records, we were able to identify all-cause absences and episodes of clinical malaria among all workers, as well as identify the time since the most recent IRS episode before the onset of absence or illness.

Worker characteristics, illness and absenteeism data, along with IRS activity data (when each house was sprayed and with which chemical), were systematically collected, stored, and used at the individual level by the company, and therefore of generally high quality. Because cost data was less systematically collected by Maragra, and because many costs could not be precisely quantified due to the abundance of in-kind and cross-departmental expenditures, we had to rely on estimations based on a mix of interviews, receipts, and interpolations. Additionally, wage data for some employees in higher-level positions was not available due to privacy concerns. Since our program cost data is not as reliable as our worker

characteristic and outcome data, we were conservative in our estimates, and generally tried to err on the side of inclusion when doubt was aired regarding whether to include program activities and materials into program costs. Cost data consisted of three types: (i) wages of malaria control employees, (ii) transportation and vehicle costs for IRS teams, and (iii) acquisition costs of purchasing IRS chemicals for fumigation (ACT and DDT).

Descriptive statistics

We collected absenteeism and demographic data on 3,915 workers with known residence from 2013 through 2016. Workers were approximately 60% male, and 75% fieldworkers (the remaining being mostly factory and administrative workers). Most were in their 20s and 30s (72%) and employed on temporary contracts (76%). Temporary workers tended to be younger and male; female temporary workers being on average 5-10 years older than their male counterparts. Permanent workers had a bi-modal age distribution, the older peak explained by the greater density of males in administrative roles. Females accounted for 43% of temporary workers but only 16% of permanent workers. Due to a lack of data availability regarding contract end dates in 2016, and data reliability issues for 2013, we had to exclude from our analysis all temporary workers for the years 2013 and 2016. The breakdown of the number of observations for different demographic / worker groups in Table 1 (below) differs slightly from the above since the unit of observation in the table is worker-days, rather than workers.

	2013 (n=276650)	2014 (n=439387)	2015 (n=559352)	2016 (n=261101)	Overall (n=1536490)
Worker location					
Field worker	103674 (37.5%)	240043 (54.6%)	339467 (60.7%)	79715 (30.5%)	762899 (49.7%)
Not field worker	172976 (62.5%)	199344 (45.4%)	219885 (39.3%)	181386 (69.5%)	773591 (50.3%)

Worker contract		2013	2014	2015	2016	2017
Permanent	276650 (100%)	282413 (64.3%)	289602 (51.8%)	261101 (100%)	1109766 (72.2%)	
Temporary	0 (0%)	156974 (35.7%)	269750 (48.2%)	0 (0%)	426724 (27.8%)	
Worker sex						
F	46192 (16.7%)	86319 (19.6%)	132532 (23.7%)	41756 (16.0%)	306799 (20.0%)	
M	230458 (83.3%)	353068 (80.4%)	426820 (76.3%)	219345 (84.0%)	1229691 (80.0%)	

Table 1. Observed worker-days by year and worker characteristics.

During the study period, weather followed typical seasonal trends for the area, albeit slightly drier than previous periods.

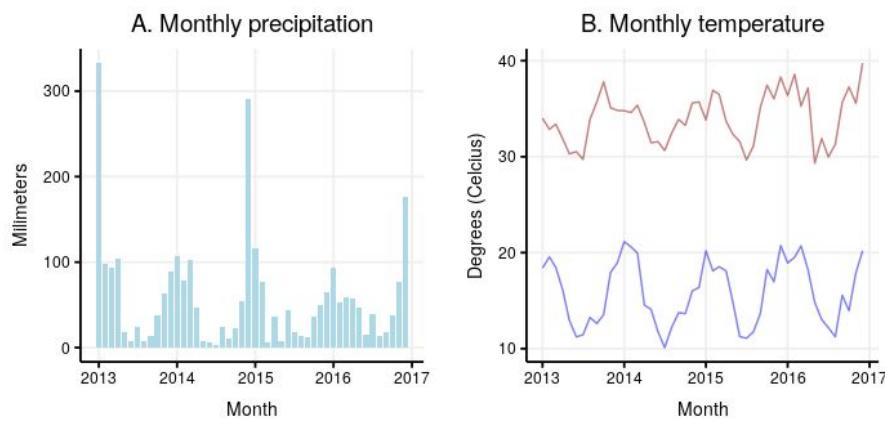


Figure 2. Monthly total precipitation in the Manica district; B. Monthly maximum (red) and minimum (blue) temperatures.

In Southern Mozambique, malaria peaks during the summer months (December through March) most years (Figure 2, panel A), and worker absenteeism rates (figure 3, panel B) track district-level malaria incidence (Figure 3, panel A) closely, following the same seasonal weather patterns (figure 2, panel B). Both all-cause absenteeism and sick absenteeism have declined in recent years at Maragra (figure 3, panel C), with the latter declining at a faster rate than the former. The fact that the rate of

confirmed cases at the company clinic is largely non-seasonal (figure 3, panels E and F) suggests that a significant portion of workers either seek care for malaria elsewhere (for example, government health posts, of which several are nearby and in some cases closer to workers' residence than the company clinic) or do not seek care at all during malaria infection. Accordingly, we focus our analysis on all-cause absenteeism rather than sickness absenteeism or malaria diagnostics, with the assumption that much of illness is captured by absenteeism but not by the clinical data.

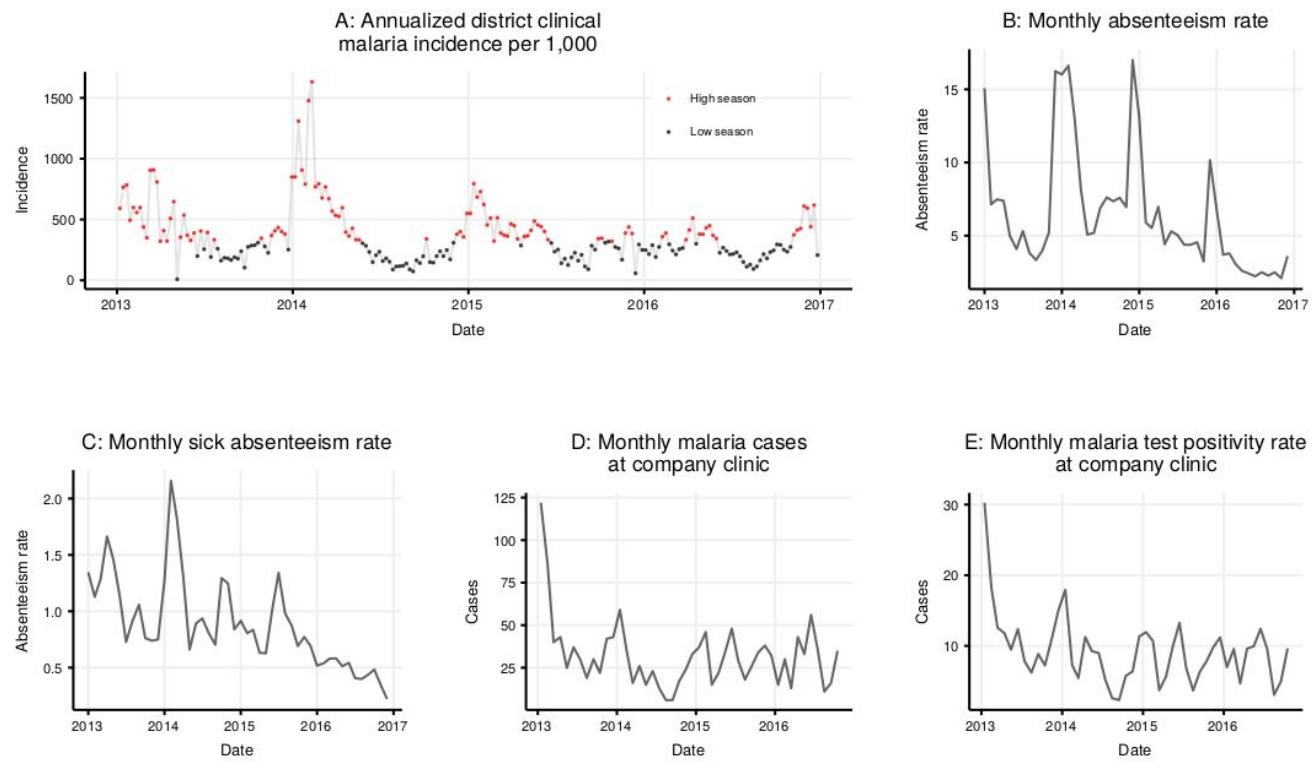


Figure 3. (A) Clinical malaria (district of Manhiça), (B) all-cause absenteeism among Maragra workers, (C) sick absenteeism among Maragra workers, (D) positive cases at company clinic, and (E) test positivity rate at company clinic

Fumigations: During the period from January 1st, 2013 through December 31st, 2016, the Maragra Malaria Control Unit carried out 11,007 episodes of fumigation of residential “agregados” (households), for a total of 13,260 building-fumigation combinations. The total number of unique agregados sprayed during this period was 3,998.

	2013	2014	2015	2016
Households fumigated	1170	2336	2963	2019
Fumigations	1235	3283	4303	2186
Percent of households fumigated	28.92	57.73	73.23	49.9
Mean fumigations per fumigated household	1.06	1.4	1.45	1.08

Table 2: Fumigation activity by year

IRS activities, managed by Maragra’s Malaria Control program, are ongoing throughout the year, albeit with significant variations in activities by month (Figure 4, panel i). Most on-site houses are sprayed, though the time between fumigations is irregular (Figure 4, panel ii). Off-site houses may also receive IRS (managed and carried out by the National Malaria Control Program), but the status and timing of these fumigations is not known at the individual level. Though we do not have data on the non-residential workers (who we consider as the “business as usual” control group), they are included in our models because they provide useful information pertaining to the effect of seasonality.

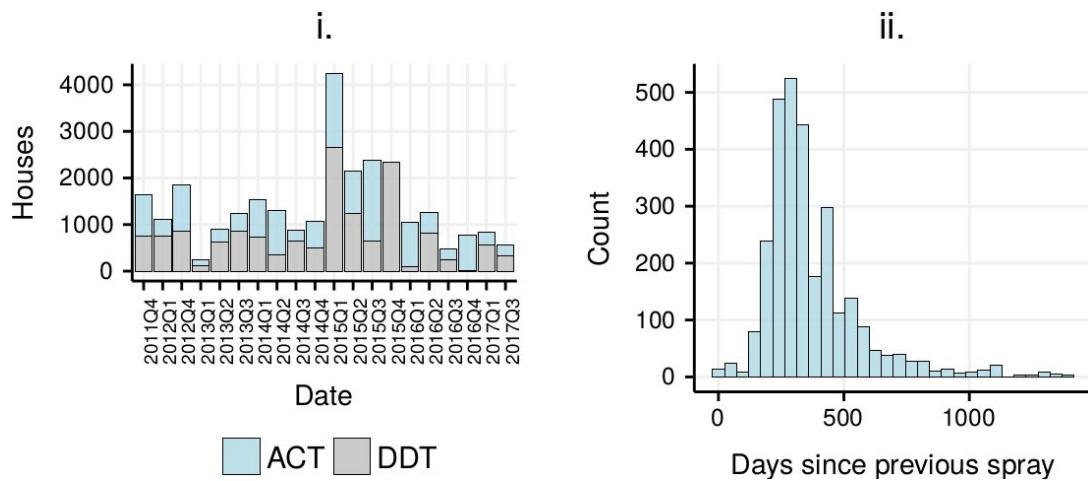


Figure 4. (i) Fumigation activities carried out by Maragra Malaria Control during study period, (ii) Distribution of average time between sprayings of households

Costs of program: The malaria control program at Maragra has an average annual operating budget of approximately \$76,500, which includes the purchase of insecticide, the wages of IRS sprayers and drivers, transportation, record-keeping, and general administrative costs. Assuming linearity in costs, the program spends approximately \$23 per building sprayed¹. Much of the benefit of IRS goes to non-worker residents (such as family members) of sprayed agregados (who constitute a majority), but this benefit is purposefully ignored for this analysis, since our focus is solely from an internal accounting (ie, profit) perspective. Costs by category varied widely by year (figure 5).

¹ \$76,500 is the average total Malaria Control department's budget for the years observed. \$23 is the result of dividing the average number of households sprayed into the budget.

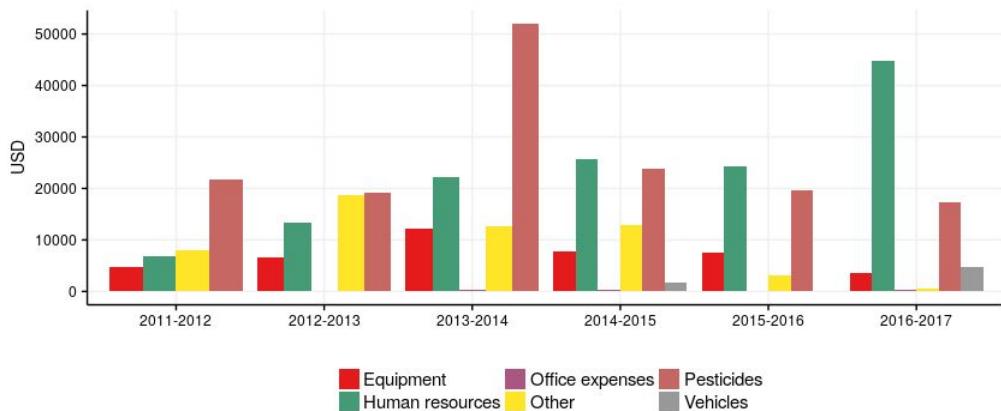


Figure 5: Operating expenses related to the malaria control program

Cost of malaria: Given the fact that clinical data does not fully capture all malaria-related absences (both for the possibility for workers to go to non-company public health clinics in the area and for looking after family members who have malaria), our main focus on quantifying the costs of malaria is through excess all-cause absenteeism. For the purpose of simplicity, and lacking a better measure of productivity, we simply consider that an absence costs the company the wage of that worker. For clinical savings, we estimate the number of absences which result in one positive clinical malaria case at the company clinic (80), apply the estimated treatment cost (\$31.49 as per (Ezenduka et al., 2017)) to the equivalent share of prevented absences, and convert that figure into a daily cost. We intentionally ignore the savings accrued by the public health system, as well as the likely utility gains in secondary realms such as school absenteeism, productivity, etc.

Conceptual framework and identification strategy

Our aim was to estimate the effect of IRS on worker absence. By extension, we calculate return on investment. Our data allow us to link fumigation data at the

household level to the absence rates of workers residing in that household. The protective effect of IRS on an individual residing in a fumigated household is assumed to be highest upon spraying and declines thereafter over the course of 12 months, at which time we consider the house to no longer be protected. This waning effect in protection is attributable to declines in a mosquito's likelihood of dying upon contact with a surface treated by IRS as well as the likelihood of being deterred from remaining in the area. Experimental observation of compounds treated by pyrethroids, ie ACT (Sherrard-Smith et al., 2018) shows that the waning effects in mosquito mortality and deterrence translate to a similarly quasi-linear increase in successful bloodfeeding episodes over the course of approximately one year. Our linear decay function for IRS' effectiveness assumes that DDT's effectiveness follows the same temporal patterns as ACT's, and fails to take into account insecticide resistance or potential interaction effects with ITN use, an interaction which has been shown in other studies to have important effects (Choi et al., 2019; Protopopoff et al., 2018). By the same token, this approach ignores potential compounding effects of IRS application over time as a function of timing relative to the malaria transmission season (Worrall et al., 2006), and does not take into account surface material, which may also impact insecticide effectiveness (Ngwej et al., 2019). Though only a rough proxy, our estimation for the function of the waning effect of IRS insecticides is in line with research based on direct observation of mosquito mortality (Tangena et al., 2013) as well as indirect observation of effectiveness based on the incidence of mosquito-borne illness (Bradley et al., 2012).

Since the presence of nearby IRS (even if not at one's own house) reduces the number of living nearby mosquitoes, we also consider the fumigation status of neighboring households as a protective factor against malaria infection. In other words, IRS application at one house has a positive externality at other nearby houses. This "spillover" effect would theoretically go through two channels: (i) via a reduction of mosquitoes in the vicinity and (ii) via a reduction of the malaria parasite in the blood of humans in the vicinity (ie, the parasite "reservoir").

In order to account for the fact that applying IRS has (i) a direct effect on the recipient (when the IRS is applied to the walls of his/her home), (ii) an indirect effect on the participants neighbors, and (iii) a waning effect over time, we devise a time-specific "protection" score based on the theoretical effectiveness of IRS, and then use that protection score to develop a time-place specific "community protection" score based on a weighted average of nearby household protection scores. We consider a household's "community" protection level (ie, the protection conferred to the house through externality) to be the contribution of the other houses' protection levels, weighted by the distance to the house in question. This approach, though failing to take into account the complex relationship between vector abundance and human density (Romeo-Aznar et al., 2018), accounts for the fact that fumigation of a household kills mosquitoes which otherwise would have made it into other nearby households.

We define community protection status as...

$$p_{it} = \sum_{j=1}^{N_i} w_{ij} F_{jt}$$

wherein...

$w_{ij} = \frac{1}{1+D_{ij}}$, where D_{ij} is the distance between household i and j in meters

$F_{jt} = \max(0, 365 - \text{nr of days since fumigation of household } j)$

N_i = the number of households living in a 1 km radius of household i

An individual's total protection score at any given time is the sum of the indirect protection conferred by fumigating neighbors' households and the direct protection conferred by the fumigation of her household. The decision to devise a score for indirect protection conferred by others was motivated in part by findings from previous studies on positive health externalities in malaria interventions related to bednet coverage (Alaii et al., 2003; Escamilla et al., 2017; Stebbins et al., 2018). Our score is conceptually similar to Cohen and Dupas' quantification of the positive externalities of bednet use in Kenya (Cohen and Dupas, 2010) in that it attempts to estimate the protection conferred to "non-users" by "users" and is in line with Hawley et al's finding that the main driver of reductions in malaria following bednet distribution was not sleeping under the net, but rather the community-wide reduction in mosquitoes (Hawley et al., 2003). Though no studies exist on positive externalities for IRS coverage at the individual-level, to the extent that the mechanisms for the reduction in infection are similar to those of bednet (reduction in the natural reservoir of the disease, reduction in the number of nearby vectors, etc.), it is reasonable to assume similar effects. Our approach for estimating indirect effects of IRS differs from Hawley's estimation of bednets' indirect effects in that we incorporate a time

dimension for the intervention's waning effect, requiring us to create community protection scores for every day-location pair. Also, unlike other studies which conceptualize community protection as a function of coverage in an area with an explicit cut-off (ie, 300-meters from the household in the case of Hawley, a cluster, village, or compound in most other cases (Stebbins et al., 2018)), and treat equally the relative contribution to indirect protection of all units within that cut-off, we aim to increase precision by weighting each neighboring households' contribution to any other household's indirect protection score by distance, with an intentionally high cut-off of one kilometer. Though there is no literature on the relative contribution of the indirect protective effect of an intervention on a very nearby (40 meters) versus far-off (300 meters) household, it is biologically reasonable to assume that the former is greater. The choice of a high cut-off (1 kilometer) was motivated in part by the fact that individual mosquitoes have been found to travel significant distances: a 2019 study, albeit of a different sub-species, found an average distance of nearly a kilometer before re-trapping, with some mosquitoes having traveled 3 kilometers from their release site (Webb and Russell, 2019). Both direct and indirect protection were assigned a value on a 0 to 1 scale, with 1 being maximum protection (the day of IRS) and 0 being unprotected (never fumigated or >365 days since fumigation). These values were then decayed by time since fumigation ((365 - days) / 365) and weighted for each observation by the distance to the area estimated (1 - distance in kilometers). The protection score is the simple sum of the community and individual protection values.

Lagged precipitation is an important determinant of malaria activity. Though some studies use relatively long lags (as many as 4 months, (Matsushita et al., 2019;

Stebbins et al., 2018)), most have found that a 1-2 month lag is sufficient for predicting malaria outbreaks (Jusot and Alto, 2011; Matsushita et al., 2019; Stebbins et al., 2018; Wardrop et al., 2013), especially in relatively warm climates. Accordingly we employed a 15-60 days rolling lag of cumulative millimeters of precipitation.

Econometric model

Our model specification is intentionally simple. We understand the risk of absenteeism to be influenced by two factors: malaria seasonality (captured in our lagged precipitation term, which spans from 15 to 60 days prior to the date in question) and "protection" (ie, the time-specific summed IRS in the vicinity, weighted by distance, as described in the previous section), and can be conceptualized formulaically as follows:

$$\log(1 + Y_{it}) = \beta_0 + \beta_1 IRS\ protection_{it} + \beta_2 Precipitation\ lag_t + \alpha_i + v_{it}$$

Y_{it} is the probability of absence at time t for individual i. $IRS\ protection_{it}$ is the worker's day-specific "protection" level as conferred by the IRS status of her and others' households as well as her own household's fumigation, and $Precipitation\ lag$ is 15-60 day lagged cumulative precipitation. α_i represents the time invariant worker fixed effects. v_{it} is the error term.

We assume that the marginal benefits of IRS are likely to be different for different worker types. Fumigation can be reasonably expected to be greater for those who spend more time in that area (ie, permanent workers). By the same token, those with higher socioeconomic status are likely to benefit less from fumigation because of the fact that they are more likely to have available other malaria prevention measures

(screened doors and windows, repellents, air conditioning, insecticide-treated nets).

It is plausible that different worker roles (field vs factory, for example) may have differential exposure to malaria-transmitting mosquitoes based simply on the amount of time spent outdoors. Finally, it is reasonable to assume that the effect of IRS on preventing absence might be greater among those who reside continuously in the IRS-treated area (permanent workers) than among those who reside there intermittently (migratory temporary workers). Given these probable differences in IRS' effect by worker type, we estimate the model separately for three distinct groups: (i) permanent field workers; (ii) permanent non-field workers; and (iii) temporary workers

Our approach towards return on investment (ROI) can also be described in a straightforward fashion...

$$R = \frac{P_w - S_{wa} - S_{wc}}{P_w}$$

...where R is the return on investment, P is the malaria control program's total operating cost, w refers to costs at the per-worker level, S is saving, a refers to savings through avoided absences, and c refers to savings through avoided clinical encounters. We define the malaria control program as "profitable" from an investment standpoint if ROI is greater than 100%, ie if the savings associated with the estimated effect of IRS in prevented absences and reduced clinical costs is greater than the costs of the program's administration.

Reproducibility and ethical approval

All data processing and analysis were carried out in R (R Core Team, R: A language and environment for statistical computing) and all analysis code is freely available online (Brew, 2017). Ethical approval for this project was obtained from the Institutional Ethics Review Board for Health at the CISM (CIBS-CISM) prior to data collection.

4. Results

Effect of IRS on absenteeism

Figure 6 shows average monthly absenteeism as a function of time before and after IRS application. Immediately following IRS at one's own household, a worker's likelihood of absence drops significantly (figure 6, panel A). As one would expect if the mechanism by which IRS reduces absence is through reduced malaria infection, the effect of IRS during the low transmission season is significant, but far less substantial in effect size (figure 6, panel B).

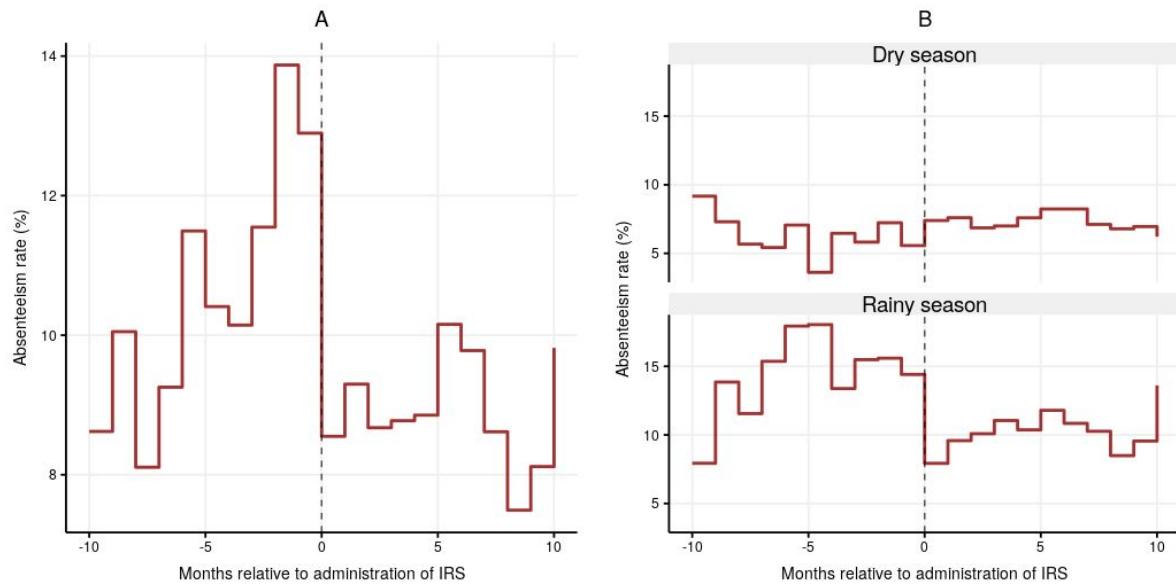


Figure 6 (i) Absenteeism before and after IRS administration for all workers who ever received IRS, (ii) The same, but segregated by rainy and dry seasons (defined here as above or below the median value of lagged precipitation)

Separate models were estimated for all 3 worker groups, and a fourth model was estimated with all groups combined. Model results (table 4) show that there are two clear archetypes. Among permanent workers, IRS administration is associated with a significant reduction in absenteeism, whereas this relationship is directionally ambivalent and statistically insignificant among temporary workers.

	Permanent field workers	Permanent non-field workers	Temporary workers	Non-segregated model
IRS protection	-0.028 ($p = 0.001$)	-0.035 ($p < 0.001$)	0.006 ($p = 0.43$)	-0.026 ($p < 0.001$)
Lagged precipitation	0.009 ($p < 0.001$)	0.005 ($p < 0.001$)	-0.002 ($p < 0.001$)	0.005 ($p < 0.001$)

Table 4: Linear fixed effects model with 1,933,715 observations, $p < 0.001$,

R-squared of 0.076.

A more intuitive presentation of the reduction in risk of absenteeism associated with our model estimation than the above coefficients is the generation of predictions of absenteeism as a function of protection score, setting the other predictors (lagged precipitation and the worker-specific fixed effect) to the average for the entire study period and population, respectively (figure 7).

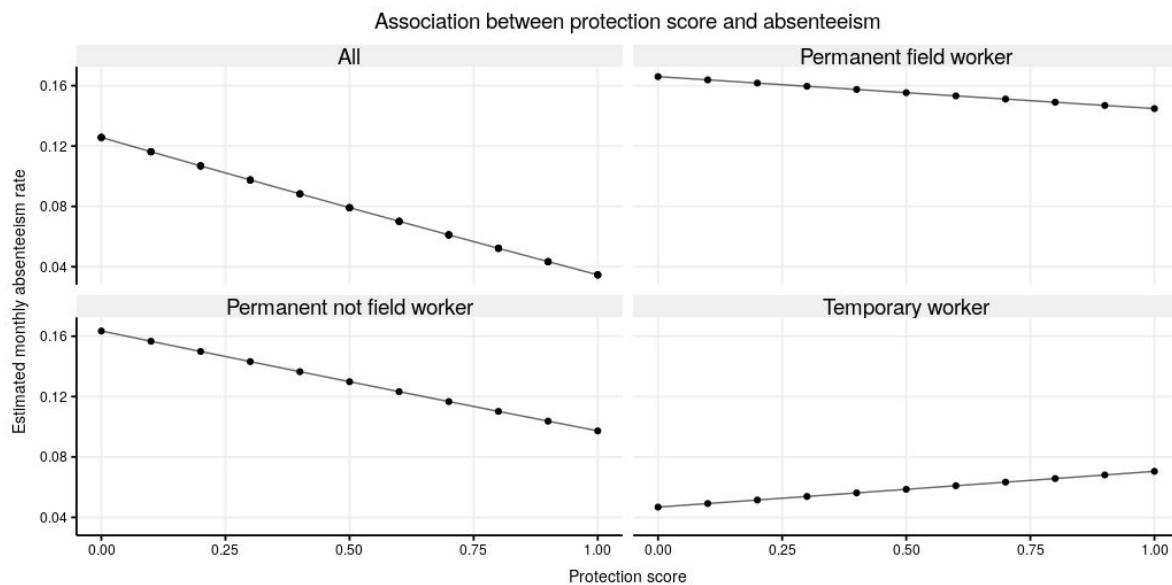


Figure 7: Predictions for absenteeism as a function of individual protection (color of line) and community protection (x-axis)

By the same token, we use predictions on simulations to estimate absenteeism as a result of different fumigation "strategies", including the counterfactual of no spraying at all (which, when juxtaposed with the observed absenteeism during our study, can be understood as the effect of the program itself).

The number of absences prevented by Maragra's IRS program can be understood as the number of absences which would have occurred had the program not existed minus the number of absences which did occur. We estimate the "would have"

scenario by simply setting all worker “protection” scores to 0 (ie, as if neither they nor their neighbors received any IRS protection), and then generating predictions using the linear fixed effects model previously described (

$\log(1 + Y_{it}) = \beta_0 + \beta_1 IRS\ protection_{it} + \beta_2 Precipitation\ lag_t + \alpha_i + \nu_{it}$, wherein all right-hand side variables are known from the previous model estimation, and B_1 is set to zero). In reality, this is over-stylized: the government carries out occasional IRS campaigns which would provide some protection to some workers. Nonetheless, ignoring the government programs is compatible with the hypothetical counterfactual from an investment perspective (ie, some IRS exposure due to government programs constitutes "business as usual").

The panel consisted of 1,933,175 worker-days. For the purposes of estimating the model, we removed observations from workers who lived off-site (cognizant of the fact that workers living at the perimeter of the site likely benefited indirectly from the firm's IRS activities). Of the remaining 588,205 eligible worker-days, we observed 60,452 absences (an absenteeism rate of 10.28%). Using the above approach, we estimate that we would have observed 84,815 absences had it not been for the firm's IRS program, for a total of 24,363 avoided absences. This translates to an overall reduction in absenteeism from 14.4% (without its IRS program) to the observed 10.28%.

Our panel was imbalanced in that it underrepresented temporary workers' true share of working days, since temporary workers' observations were removed for 2013 and 2016 (see "Methods"). This has an inflationary impact on the absenteeism reduction estimate since the absence-preventing effect of IRS is greater among permanent

workers. To offset this bias, we estimate year-specific reductions in absenteeism for each type of worker, and then weight those averages by the corresponding share of working days for the years for which full data is available. Doing so suggests an average annual reduction in absenteeism from 16.8% to 12.6% among permanent fieldworkers, a similar reduction of 16.4% to 11.4% among permanent non-fieldworkers, and a less significant reduction in absenteeism from 5.4 to 4.1% among temporary workers. Overall, given the firm's make-up of days worked by worker category, this equates to a total of 6,475 averted absences per year, a reduction from a counterfactual 13.0% absenteeism (were the IRS program not to exist) to the observed 9.3%. In total, the program is estimated to have prevented on average 1 absence for every 27 worker-days.

Return on Investment

We divide program costs by the number of prevented absences to estimate the cost per prevented absence. The average annual operating budget of the firm's malaria control program is 68,984 USD. Divided by the approximately 6,475 avoided the program is estimated to avoid annually, the firm's cost per absence avoided is approximately \$10.65. However, it is important to note that averted absences were not randomly distributed: the absence-preventing effect of IRS is higher in permanent workers (who are also more highly paid) relative to temporary workers, not only at the individual level but even more so when aggregated because (a) the total number of eligible worker-days is greater among permanent workers, and (b) the baseline absenteeism among permanent workers is greater.

Wage data was only partially available from the firm. Wages for certain “grades” (skilled workers and management) were not available, and in some cases worker grades themselves were missing in the administrative data. Accordingly, we cannot carry out an exact estimation of productivity losses using person-level wages as a proxy for productivity. Instead, we carry out a sensitivity analysis of return on investment as a function of the productivity (ie, daily wage) of temporary and permanent workers (figure 7), aggregating both permanent field and non-field workers given the similarities in the estimated effect of IRS on each groups' absenteeism.

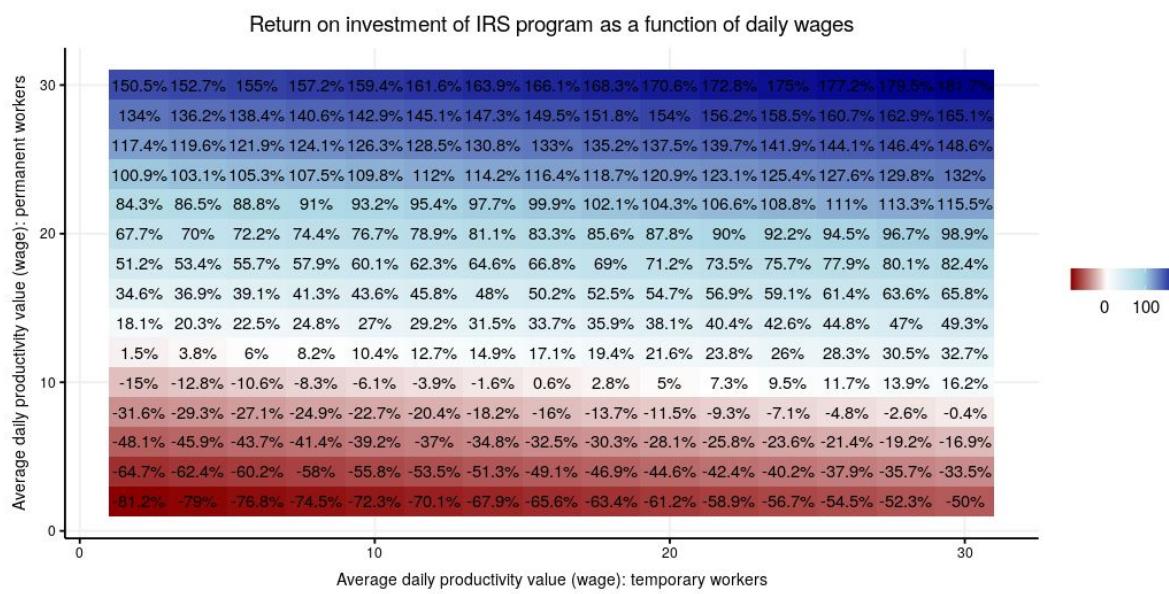


Figure 7: ROI as a function of daily estimated average productivity of temporary and permanent workers, given Maragra's ratio of temporary to permanent workers.

Of course, the above is subject to the percentage of workers of each type. Relative to many firms, the percent of eligible working days at Maragra among permanent

workers is quite high (68%). Figure 9 shows different scenarios in which that ratio were to change.

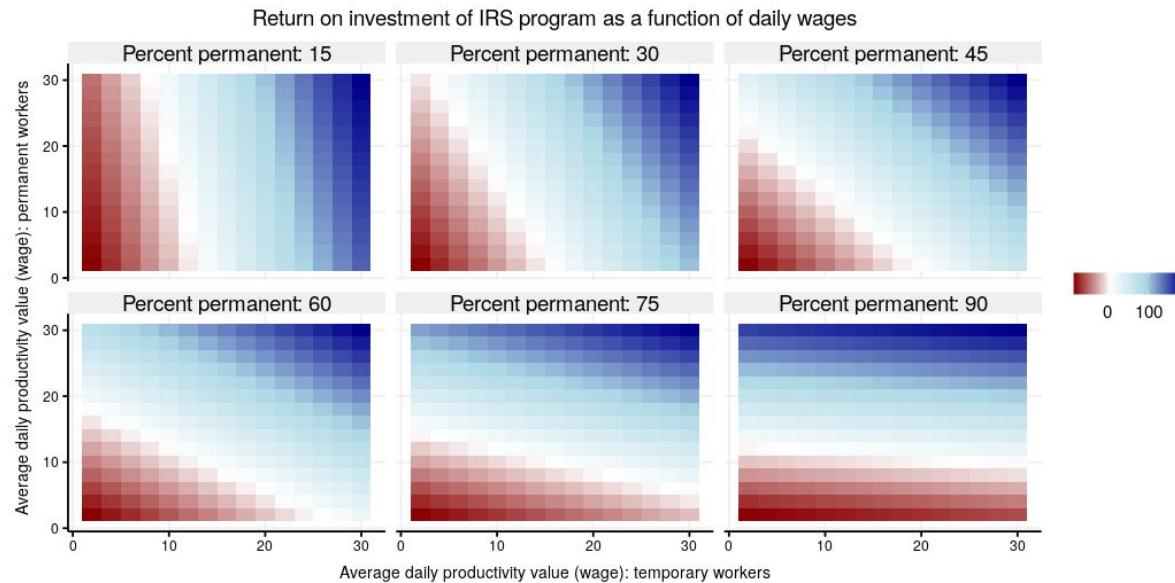


Figure 9: ROI as a function of daily estimated average productivity of temporary and permanent workers, given Maragra's, faceted by percentage of workers which are permanent

Given the non-random missingness in wage data, there is no way to estimate exactly whether the firm's IRS program is associated with a positive ROI. However, given that the large majority of temporary workers are cane-cutters, who earned on average \$5-9 USD per day, for the program to be profitable, average daily productivity (ie, daily wages) among permanent employees would have to be approximately \$10 USD or less. This does not take into account the fact that, on average, for every 80 absences, the firm's clinic treats a case of malaria, with a cost of treatment estimated to be \$22 (\$0.28 per absence).

Alternative scenario analysis: policy simulations

In previous sections, we showed that the counterfactual of no firm IRS operations would have lead to approximately 6,475 additional annual worker absences over the course of the four year study period. However, though the most useful for calculating ROI, the “zero” IRS strategy is not the only plausible counterfactual. Two others also exist. First, one could employ a “time-optimized” strategy in which an identical amount and chemical distribution of total insecticide is used, but deployed in such a way that “overprotection” (ie, more than 1 spraying in a 6 month period) does not take place and the saved insecticide is applied to houses which were “underprotected” (ie, more than 6 months had elapsed since the last fumigation). Second, a “gold standard” strategy could be employed in which no house were ever permitted to enter into an “underprotected” status, even if this meant using more insecticide.

Relative to the counterfactual absenteeism rate of 13% associated with no IRS program, the marginal benefits of the hypothetical optimized policies did not show significant improvement of the observed reduction in absenteeism to 9.3%. The “time-optimized” approach was estimated to reduce absenteeism to 8.9%, whereas the “gold standard” approach would have further reduced absenteeism to 8.8%. The fact that the marginal gains from optimizing IRS timing are minor suggests that there may be an unobserved “wisdom” in the current practice of non-systematic fumigation operations, such as timing based on local epidemiological conditions or identification of other risk factors.

The “gold standard” strategy (ensuring all on-site households were < 6 months from the most recent fumigation at all times) would have led to the greatest reduction in absenteeism. Its similarity to the “time-optimized” strategy can be explained by unnecessary re-sprayings. In other words, by simply re-allocating the insecticide used for the approximately 45% of fumigations which occur at a household which had already been fumigated in the previous 6 months, a situation similar to the gold standard could be achieved using an identical amount of spray. It is worth noting, however, that the “gold standard” strategy of 6 months re-application is based only loosely on estimates of insecticide decay (Sadasivaiah et al., 2007) and any policy recommendation stemming from these simulations should first be field-tested.

Robustness and generalizability

Three principal concerns call into question the results of our analysis. First, the application of IRS to a worker’s house may be endogenous. It is reasonable to suspect that the assignment of IRS to households is not random, but rather that IRS was applied more frequently to houses which had already seen a malaria case. In this case, our estimated effect of IRS on absenteeism would likely be underestimated, with the post-IRS absenteeism rates actually having declined from a greater pre-IRS absenteeism rate than otherwise suggested.

To check for this, we estimate the odds of absenteeism as a function of receiving IRS 10 days in the future. If IRS applications were indeed endogenous, we would expect absenteeism to be elevated during this period (since the increase in absenteeism would be theoretically responsible for the application of IRS), a situation which would require further statistical adjustment. If, on the other hand,

there is no endogeneity, we would expect absenteeism in the 10 day period prior to IRS administration to be similar to other pre-IRS absenteeism (adjusting for seasonality and job type, etc).

The below shows our robustness check for all cause absenteeism.

Variable	Estimate	Lower	Upper	P value
(Intercept)	0.0662	0.0614	0.0711	< 0.001
10 days prior to IRS	0.9229	0.7300	1.1503	0.489
Malaria season	3.1173	2.9319	3.3156	< 0.001
Department: Factory	1.0944	1.0118	1.1841	0.025
Department: Field	0.5426	0.5036	0.5850	< 0.001
10 days prior to IRS:Malaria season	0.8172	0.6161	1.0908	0.165

The large P-value associated with the 10 days prior to the IRS variable's association with absenteeism suggests that endogeneity is not a significant concern.

The second concern is that our quantification of return on investment is distorted by the fact that we treat IRS operations as essentially linear in nature, when in reality economies of scale, in-kind purchases and other factors likely make the true cost-per-spraying convex. To the extent that this paper examined only one company - and not during a time of operational change - we cannot make any reliable inference regarding how costs would be expected to change as a function of program characteristics.

The third concern regarding robustness is our estimation of the IRS protection score. Our analysis assumes that the degree of protection conferred by fumigation declines

linearly as a function of distance up to 1 kilometer away. In other words, the weight of a household 200 meters away is twice that of a household 600 meters away (weight being $1000 - \text{meters} / 1000$). We believe that this approach better reflects actual indirect protection than the “hard borders” approach used in most studies, in which either a distance threshold is established, or natural village borders are used, to define an “in” versus “out” area for what constitutes community protection. That said, in order to see if our results were robust to the method used, we carried out the same analysis using a radial threshold of 400 meters. Though the magnitude of the coefficient for community protection is greater in the hard-threshold approach since it is effectively a binary variable (“in” vs “out”), the estimates are directionally similar for all groups using both the distance-weighted and hard-threshold (radial) approaches. This is consistent with the method being robust to minor changes in measurement.

5. Discussion and conclusions

We estimate that Maragra’s IRS program reduces absenteeism among workers by 3.7 percentage points (from 13.0% to 9.3%), and that the savings in terms of productivity outweigh the costs, with a program-wide return on investment of 100%, assuming daily wages of temporary workers to be approximately \$7 and permanent workers to be approximately \$10. Our analysis was intentionally restrictive. Though much of the benefits of preventing malaria are accrued outside of the firm (savings to the public health care system, improvements in health and well-being, increases in societal economic efficiency and capital accumulation, etc.), we ignored these benefits, focusing only on those savings which accrued directly to the firm. This point

of view - the narrow, profit-driven perspective of an "investor" - is at odds with the public health mindset, and most of the research on the economics of malaria. In fact, when the profit perspective is not ignored (as it usually is by public health researchers), it is criticized - often rightfully so - for failing to appropriately quantify the full costs of poor health.

But the investment perspective is useful. From the societal point of view, an investment perspective helps to identify those "win-win" opportunities in which improvements in health don't come at a cost to the public sector. From the narrower firm's point of view, a quantification of return on investment helps companies to identify those opportunities where corporate social responsibility and loyalty to shareholders intersect. And to the extent that profits and social good don't always neatly coincide, identifying situations in which social responsibility has a negative return on investment is critical to informing policies around subsidies and to quantifying them efficiently.

To our knowledge, this is the first study which has quantified ROI of privately-managed malaria control activities from a firm/investment perspective. This contributes to the body of knowledge regarding the economics of malaria both methodologically (by structuring an identification strategy which allows for the quantification of in-firm positive externalities, ie. immunity conferred upon neighbors through the application of IRS) as well as conceptually (restricting analysis to a profit-centric perspective solely).

We believe that this study may have implications both for policy and business. The fact that ROI was positive may incentivize firm shareholders to take a less cautious

approach to malaria control. By the same token, policymakers should consider working with private firms to ensure best practice in regards to the administration of malaria control programs, since both stakeholders (the firm and the public which policymakers represent) stand to benefit. The potential for a positive ROI should have particular impact in contexts in which private firms cover large areas and employ many people. This is the case not only in Maragra, but in the African sugar industry generally, as well as other agricultural and extractive industries.

Governments should work closely with firms with the shared goal of generating a return on investment to both the public and the private stakeholders. In areas where malaria control stands to be profitable from a private perspective, public resources could be restricted and appropriately directed elsewhere (areas where, due to the conditions, sparseness, or level of endemicity, malaria control is unlikely to be profitable).

Limitations

Our study is not without limitations. Our identification strategy was simple, using only two explanatory variables (protection and lagged precipitation), both of which relied on assumptions for their abstraction. Our protection variable combined an assumed linear decay in IRS' effectiveness over time with a similar assumed decline in its effectiveness over space. Both assumptions are based loosely on the literature regarding IRS's waning effect and mosquitoes' geographical range, but are almost certainly too simplistic.

We quantified absences, but data were not reliable enough to quantify productivity in finer terms. Tonnage of sugar processed would have been a more precise outcome,

and would yield more direct estimates of return on investment. But firm data on processing was too aggregated to be of use for our modeling approach. And even if it were available, tonnage as a proxy for productivity would only be applicable to cane-cutters. Since we modelled absenteeism only, we may actually be *underestimating* the true effect of IRS on productivity, since it is reasonable to think that a worker who is ill may occasionally show up to work, but work in a less productive manner. By the same token, it is plausible that productivity losses at the aggregate level are greater than the sum of their parts: a missing worker on a factory assembly line may reduce the productivity of his colleagues, for example.

Though the sample size and window of observations were large, external generalizability is difficult to assess. Our distance-based method of quantifying community protection of IRS means that our estimates for ROI for any other context would be different, based on the density of the workers' residences. On the one hand, this is a strength of the approach: it means that both (a) timing and location of IRS application can be optimized and (b) identification of profitable vs. non-profitable IRS situations can be carried out *a priori*. On the other hand, the approach does not lend itself to straightforward "translation" to non-academic business settings, where ROI is best expressed in per unit terms.

Given the global push for malaria eradication, new approaches, opportunities, collaborators, and strategies need to be identified. Scaling up private sector involvement in fighting malaria may be an effective approach - in certain areas where due to geography, resources, or other reasons - the public sector has not been able to stem the tide of the epidemic. A private sector scale-up, though, requires hard

evidence of the potential profitability of malaria control activities. In the case of this study, the evidence suggests that doing well and doing good can go hand-in-hand.

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10. Discussion and conclusions

The main question addressed in this thesis was: what are the incentives for and against malaria control and elimination-related activities? This dissertation examines the question through both observation (of private actors engaged in malaria control at the levels of the firm, health programmes, and country) as well as direct inquiry (of malaria researchers and recipients of malaria control interventions).

10.1 Discussion

The existence of incentives:

At the organization level, ample incentives exist to engage directly in malaria control. The most clear example of the evidence of incentives is the fact that the Maragra vector control program was profitable even from a purely financial perspective (ie, not taking to account any benefits in human wellbeing). Additionally, there are direct and indirect economic benefits for firms in regards to public relations when they engage in malaria control, as evidenced by the presence of both foreign and domestic firms engaging in such activities despite not having a clear internal reckoning of their economic payoff.

At the individual level, uptake of and compliance with low-cost interventions appear high, as demonstrated in the Gambian bednet usage evaluation. This itself suggests that individuals are sufficiently incentivized to self-protect, thereby contributing to the positive externality of malaria control.

The insufficiency of incentives:

Though incentives to engage in malaria control exist, it is clear that incentives alone are not sufficiently abundant, clear, or aligned to motivate scaled-up and coordinated control efforts which could amount to country-level or regional elimination in endemic countries. For example, most corporate social responsibility activities from foreign firms in Mozambique are broadly focused on general development rather than narrowly targeting malaria.

There is a high degree of scepticism regarding the likelihood of near-term success of ambitious, paradigm-shifting accomplishments (ie, eradication). Scepticism goes a long way in explaining why, despite the apparent social good returns on scaled-up malaria elimination being so great (Sachs and Malaney 2002; World Health Organization 2019), investment in elimination and eradication interventions has not been great enough to achieve those paradigm shifts. In other words, enthusiasm for ambitious investment in malaria control and elimination is tempered by scepticism over the expected value of those investments, not due to doubts over whether suppressing malaria would be widely beneficial, but rather due to doubts over the collective ability to suppress malaria. In other words, It is potentially the case that those who design social corporate responsibility programs, like the researchers who participated in the Survey of Experts study, harbor a high degree of scepticism regarding the likelihood of near-term collective “success”, and therefore optimize programs to achieve returns at a rate prior to the point of diminishing returns (Murphet and Murphet 2019).

The question of free-riding and moral hazard:

If incentives for control exist, there must be larger phenomena at play which dissuade actors from pursuing measures sufficiently ambitious to change the paradigm from control to elimination in certain regions. This would be consistent with the “common good” interpretation and the associated “free rider” hypothesis; that is, it is entirely rational for a firm to prefer that someone else shoulder the burden of the costs of malaria control and elimination efforts, leaving the firm to benefit from those efforts without the capital costs nor risk. Alternatively, at its most perverse, it could be the case that a firm’s ambitious engagement in malaria control could be so successful that it would benefit competitors or dissuade the government from investing in the health of the firm’s employees (ie, “crowding out” of other actors in the provisioning of the public good). A similar free-rider phenomenon could also be taking place at the individual-level wherein people readily engage in those malaria control activities which are of low-cost and low-burden (such as hanging a bednet to sleep in), but prefer not to engage in those activities (despite the positive externalities) if they perceive that the direct benefit is scant. The most concrete example of “last mile” elimination: once transmission is suppressed to very low levels, the individual benefit accrued from engaging in control activities is very low, and the unit cost of those activities remains identical; despite the collective benefits being high, the low cost-benefit ratio at the individual level disincentivizes sustained or scaled control activities. This dissertation did not generate any evidence pertaining to this last point, but it is consistent with a Ghanean study in which enrollment in a health insurance plan was associated with decreased bednet usage (Yilma, van Kempen, and de Hoop 2012). It stands to reason that as individuals, firms, and countries experience lower malaria incidence, the marginal costs of prevention will increase, and the direct benefits of prevention investment will be more dispersed. The game theory involved in this scenario has been studied mathematically and theorized in regards to disease elimination (Poliomyelitis and Technical Consultative Group to the World Health Organization on the Global Eradication of Poliomyelitis 2002) as well as vaccine uptake (McKillop et al. 2019).

Complexity as culprit:

Tangential to macro-level scepticism, lower-level complexity is an important culprit in the hesitancy to scale-up malaria control efforts, despite abundance of the apparent benefits. Conceptualizing risk and probability are enormously difficult and oftentimes inaccurate even at the individual level (Jumbam et al. 2020; Mnyone and Mwamundela, n.d.; Forero et al. 2014). At the level of the firm, quantifying and acting on long-term, high-uncertainty assumptions built on a scarce and ever-changing evidence base is near impossible. In this sense, the reason a firm like Maragra might engage in malaria control activities with no intention of either scaling up nor down those activities’ scope in the near future would not be because they believe they have identified the *optimal* investment-in-health spending point, but rather because they are unaware of where that point is, nor of the extent to which their current activities are costly or beneficial. This is consistent with the results of the Survey of Experts paper, where complexity was highlighted as one of the main reasons why researchers doubt the feasibility of near-term eradication of malaria. Similarly, from a financial perspective, the aptness of the complexity issue resonates in study 4 (the vaccine costing systematic review) wherein it was found that the ways by and categories in which costs are counted are incompatible both across time and space.

It stands to reason that individuals, firms, and countries are not engaged in a multi-dimensional competition with each other to see who can most benefit from the others

positive externalities, but rather are simply confused by the complexity of the malaria control problem, like specialists who research it. Complexity leads to uncertainty, which in turn leads to some degree of complacency. After all, if one is not aware of or confident in the likely outcome of an activity (such as increased engagement in malaria control), it is entirely reasonable to err on the side of trusted “experts” (Finda et al. 2020), who (as shown in study 1) are themselves sceptical over the extent to which scaled-up efforts will lead to success. This dissertation shows that complexity may be an important element hindering increased engagement in malaria control activities not because it directly affects the incentives for control or elimination, but because it makes the perception of those incentives less clear. Complexity seeps into not only the costing of interventions (studies 4 and 6), the optimizing of those interventions in complex human-animal dynamic situations (study 5), the quantification of the effectiveness of those interventions (study 3), but also the estimation of the expected value of those interventions (study 1). In turn, stakeholders engaged in malaria control and elimination-related activities (such as large foreign firms) may choose to “diversify” the corporate social responsibility portfolio, weighting more heavily towards those areas which are perceived to be less complex than malaria control and are also less binary in outcome than malaria elimination.

10.2 Question-specific conclusions

An abundance of opportunities

Where do opportunities exist for enlarging the body of stakeholders and funders involved in malaria control? It is clear from the literature that there is no shortage of areas where malaria control might be scaled up all the way towards elimination, starting with vector control (Winskill et al. 2019). Beyond the incremental progress of improved vector control strategies and compounds, the finding from the Maragra sugarcane facility, that firm-administered vector control (in the form of indoor residual spraying) not only lead to significant decreases in absence but was even profitable, could lead to a qualitative jump in malaria control activity if communicated effectively to firms. That is, if some firms were already willing to engage in malaria control without the explicit knowledge of its direct economic benefits, making those firms aware that those benefits are substantial might serve to drive them towards action (while at the same time addressing the primary insight from this research – that complexity is a major impediment to incentivization).

The opportunity to scale up involvement in private sector malaria control, evidenced by the diverse landscape of large (and well-funded) foreign firms already engaging in corporate social responsibility in Mozambique (study 2), is not limited only to Mozambique, nor should it be understood only within the narrow limits of firms engaging in vector control activities to protect their workers from infection. In fact, a wide variety of areas could leverage private sector involvement ((Bennett et al. 2017)), as long as doing so does not undermine the fundamental nature of malaria control and elimination as public goods, nor unduly concentrate risk and reliance in private hands. Though study 6 focused solely on the firm at Maragra, in areas where the cost-benefit ratio of malaria control activities were not so favorable to private investment (due to differential epidemiology, spatial density, or cost structures), public-private partnerships (PPP) may offer promise (Njau et al. 2009).

Beyond the potential for an expanded role of the private sector in malaria control, other opportunities for enlarging the body of stakeholders in malaria control exist. One important

distinction between the current era of eradication and the (failed) eradication drive of the 1950s and 1960s is that technology has substantially accelerated data collection and sharing initiatives. Accordingly, the top-down approach of the bygone era is no longer necessary since local governments and initiatives can access the same body of evidence and best practices for malaria control as those administering large international programs.

Incentive-wise, innovation could be accelerated if funding mechanisms were made available to those working at the local level. After all, a frequent theme in the survey of experts paper (study 1) was the need for localized solutions and innovation.

Lastly, and in line with the need for innovation, opportunity for scaling up malaria control exists by integrating it into multi-pronged programs whose objective is not solely malaria. If current experimental trials on using endectocide for the purposes of reducing malaria transmission prove successful (The Ivermectin Roadmappers 2020), integrating de-parasitizing programs with malaria control programs could lead to substantial synergies, particularly if geographically prioritized (study 5). The potential effect of these combinatory approaches is not a function solely of the drop in transmission from endectocide distribution via a reduction in the amount of non-lethal blood meal available to mosquitoes, but also the fact that the positive externality of the malaria control mechanism (healthier and larger cattle, in this case) would likely lead to adoption and promotion of the mechanism by sectors previously less incentivized to do so.

But a long ways to go...

What is the likelihood of and time-frame to malaria eradication? No study, however well-designed, can address this question with a high degree of certainty. Since collective reasoning has been shown to be more accurate than individual judgment in areas of high uncertainty (Hamada, Nakayama, and Saiki 2020), study 6 focuses on gauging overall researcher sentiment on the likelihood of, timeframe to, and issues associated with malaria eradication at a global scale. The results of this study suggest that malaria researchers are pessimistic regarding short-term success. This pessimism largely stems from the perceived need for innovation, complexity, and the systemic challenges of discoordination, health services systems weaknesses, lack of political will, and poverty.

Clarity on costs are needed

How much does malaria control cost? Studies 4 and 6 aimed to quantify both hypothetical and observed malaria control interventions, which were radically different in scope (all of Sub-Saharan Africa vs one firm) and method (an innovative future vaccine versus a very common method of vector control). The principle conclusion from study 4, in regards to costs, is that better data systems and protocols are required in order for programs to generate cost data which are comparable across space and time. The huge variance in cost per dose delivered suggests low internal validity.

Conversely, though each kind of cost was well-documented and categorized in study 6 (i.e., it had high internal validity), there is no evidence to suggest that the costs of fumigation at Maragra are generalizable to other locations or epidemiological contexts. The method we used to estimate the effect of IRS on absenteeism was highly dependent on the spatial density of workers, and likely dependent on the nature of the work performed and socioeconomic status of workers (insofar as the marginal protection from malaria control

programs is less when workers are of higher socioeconomic status, and can therefore afford to take more ambitious malaria prevention measures at the individual level).

The lack of clarity on costs, and the challenges in generalizing study-specific cost findings, add to the complex nature of the malaria control incentives problems. Though the evidence generated in study 6 regarding the relative benefits of malaria control activities leads to optimism, a great deal of further work is required in identifying the extent to which the case of Maragra is unique or universal. Regardless, clarity on costs is a prerequisite for expanding the body of stakeholders in malaria control.

Effectiveness

What are the effects of malaria control and elimination activities? Studies 3 and 6 provided evidence that malaria control activities have the potential to be highly effective insofar as they are met with high uptake and cooperation from the community and can be self-financing (respectively). Though neither study directly measured the vector control strategies' effectiveness in preventing malaria among those who received the interventions (ITN and IRS, respectively), both studies' findings contained elements of information which lend themselves to optimism. In rural Gambia, using a method which has been shown to de-bias responses in other contexts, it appears that bednet usage is very high. In rural Mozambique, at a sugar processing farm and facility, IRS lead to a reduction in absences significant enough to offset the costs of the program. In other words, both the bednet distribution program in Gambia and the fumigation program at the Mozambican firm were *effective* at least some of their intended objectives (providing the population with a protective measure it will use and reducing the incidence of absenteeism among workers).

Doubts about the data

However, in both of the aforementioned cases, legitimate doubts can be raised. In study 3, the method used (list randomization) had no mechanism for validation; in study 6, the endpoint used (absenteeism) was not validated by the biological mechanism (evidence of infection); that said, it is plausible that the mechanism for reducing absence is both biological (preventing infection in workers) and social (preventing infection in workers' family members, who the workers would then be compelled to provide care for instead of working). In either case, since IRS cannot be assumed to be fully random, there is no way to parse out the role of selection bias in accounting for differential absenteeism rates among members of different households (for example, there is no objective data available on IRS refusals). This leads to the final research question addressed by this dissertation: To what extent can we rely on the data generated by malaria-related research? Study 3 offers a novel, but ultimately unsatisfying (insofar as it lacks validation), glimpse at how what we observe might not truly reflect what occurs. Study 5 relies on data curated from a myriad of sources on livestock density and parasite prevalence. Though these data may be best in kind (and more rigorously and systematically collected than at any point previously), this does not mean that they are correct. On the contrary, it could be the case that the *unobserved* data are precisely those data points which are most important to malaria control (in the sense that the most isolated areas will likely serve in future as the last blood reservoir of the malaria parasite prior to eradication).

Study 6 is a unique case in that it uses firm-generated administrative data, which has the positive attribute of having a high standard for accuracy for economic reasons. That is,

beyond the research value, a firm knowing when, where and how it spends its resources is unto itself a valuable investment. Accordingly, Maragra (like many firms) has sophisticated data management platforms for tracking human resources and activities. Though the objective of these platforms is not research per se, the platform's robustness (relative to those data collection tools build ad-hoc, often with low budgets, for the specific purpose of collecting research data) is a strength. In this sense, in response to the question on the extent to which we can trust data generated by malaria-related research, study 6 offers a high degree of reliability. Accordingly, the conclusions from study 6 regarding the potential profitability of malaria control activities at the firm level, should be considered robust; though study 3 has the advantage of being experimental in nature, it uses an unvalidated endpoint; studies 4 and 5 have the limitation of a reliance on diverse and discrepant data sources; and studies 1 and 2 have the limitation of combining a mix of grey and white literature (study 2) and self-reporting only (study 1).

So, can we rely on the data we collect? Yes, but the degree of our reliance should be proportionate to the robustness of the methods and sources used. In the case of this dissertation, the most significant finding (that malaria control may be profitable in some cases) has the good fortune of stemming from the study with the most robust data.

10.3 Overall conclusions

1. Incentives for malaria control exist for private organizations. A firm engaging in malaria control activities can expect a positive short-term return on the investment, even if excluding all non-financial benefits in the quantification of the return. Beyond financial benefit, firms benefit in terms of public relations from engaging in corporate social responsibilities, including malaria control.
2. Incentives for malaria control exist for individuals. Using methods meant to minimize social desirability bias, usage of ITNs by rural Gambians was estimated to be very high, suggesting that people who are on the recipient end of malaria control interventions perceive them as sufficiently valuable so as to engage in them.
3. Though incentives for control exist, individual and organizational actors are not, or do not perceive to be, sufficiently incentivized to engage in the degree of malaria control which could lead to area-wise elimination or worldwide eradication, as evidenced by a regression in progress in recent years. The insufficiency of incentives is exasperated by both (a) significant scepticism, and even pessimism, regarding the likelihood of near-term paradigm shifts (elimination), (b) the perception of complexity in regards to the critical path towards and respective roles for achieving those shifts, and (c) an overall unfamiliarity with the core study-generated data which could inform both key performance indicators of malaria control and effectiveness evaluations.
4. Given the current insufficiency of status quo malaria control methods to accelerate progress, innovation is needed. Technical innovation is fundamental in order to outpace parasite and vector resistance, but other forms of innovation may be complementary, including both widening the body of stakeholders involved in coordinated malaria control efforts as well as enlisting combinatorial methods in which the benefits to those who partake go beyond just malaria.
5. The cost of malaria control is less than the cost of not controlling malaria, though a lack of standardized, transparent, comparable data on the costs and economic

benefits of malaria control make it so that decision-makers have to choose from a myriad of development interventions in what is essentially an opaque-pricing market, resulting in potential under-investment in malaria.

10.4 Limitations

This dissertation is not without significant limitations. The survey of malaria experts (study 1) included only academic researchers, who may be less familiar with the “real-world” challenges of malaria control than those who are purely devoted to operations. Sample size was large, but response rates were low. The proxy measurement for research impact (total number of citations) is biased in ways that go without saying. The pool of respondents was slightly different demographically than the group of researchers who rejected the invitation to participate, and though estimates were de-biased, there exists no technique for validating the quality of the de-biasing. In addition to the potential fallacies regarding how humans perceive future probabilities, the study also has the limitation of simply not delving into much depth in regards to respondents’ specific experiences, geographies, or reasons for participation. In other words, there was no mechanism (such as confirmatory questions, follow-up discussion, member checks) by which to probe further into survey responses. The resulting analysis of free text responses was therefore in some ways more similar to a document analysis than a qualitative research undertaking.

The analysis of foreign direct investment and corporate social responsibility in the malaria landscape of Mozambique (study 2) shared a limitation with study 1 in regards to generalizability: the limited use research databases. Study 1 used only PubMed to retrieve authors and their publication-related metadata, and Study 2 used PubMed and EBSCOhost. In both cases, this meant not detecting researchers who publish in journals indexed elsewhere.

The study of bednet usage among Gambians (study 3) utilized a novel technique which has never been validated. Though a reasonable reading of the results points to the technique’s utility, the internal validity of the study is questionable since biases unbeknownst to the researcher may have crept into the data elicitation method. Additionally, the study’s external reliability may be low given that it took place in an area with a great deal of prior health research. The sample size was relatively small, precluding any meaningful analysis of characteristics associated with bednet usage, and the pattern of response suggests that perhaps the list randomization method might result in a certain degree of “centering” responses to non-extremes in certain populations.

Estimating the costs of a hypothetical malaria vaccine roll-out in Sub-Saharan Africa based on existing vaccine programs (study 4) was an endeavor bound to meet certain limitations. Among them, like study 1, this analysis used the PubMed database, therefore overlooking gray literature. Additionally, incremental costs were found to be highly contingent on local capacity, making variability high (and external generalizability low). Finally, we were unable to perform financial versus economic analyses, due to the non-standardized nature of our data.

Mapping opportunities for endectocide for malaria control (study 5) had the limitation of relying purely on ecological-level data, with no incorporation whatsoever as to what was

feasible operationally, economically, or culturally. The analysis also made no attempt to quantify the environmental costs of a mass endectocide for malaria campaign, nor did it explore opportunity costs. Finally, the analysis was largely speculative, and did not fit its findings into the larger malaria eradication global campaign.

The analysis of absenteeism among sugarcane workers (study 6) assumed a linear decay in IRS effectiveness, when in reality it is almost certainly non-linear (but unknown). The study also assumed that absences correlated directly with lost productivity. Though sample size was very large, the degree to which results are externally generalizable is questionable since much of the effect of IRS (per our model) depends on the timing of fumigations and precipitation, as well as the geographic density of workers' residences.

10.5 Further research

This dissertation opens the door to several lines of research which should be carried out in the short-term. The finding that malaria researchers are more pessimistic about the prospects of eradication than their institutions merits deeper investigation, specifically in regards to the potential incentives researchers might have for not speaking their minds freely (or, conversely, the incentives institutions face to generate optimistic communication in order to attract funding). By the same token, the study's approach should be expanded to other stakeholders in the malaria-control community, outside of PhD-level academic researchers, especially those with on-the-ground knowledge and operational experience.

The results of the study of bednet usage among Gambians leads to questions both about (a) the subject area itself and (b) the methodology. In regards to the former, more research is needed on the "decay" in usage of bednets over time. Snapshot, cross-sectional estimates are useful, but insufficient for predicting when a campaign would be most useful and to whom it should target. The list randomization methodology is promising, but requires further validation before it can be used as a reliable indicator at scale. Since human-observation in the household would constitute too significant an invasion of privacy, validation study of list randomization could use direct observation via non-invasive sensors.

In order to improve estimates on the costs of vaccine programs, a standardized set of guidelines for reporting these types of costs is urgently needed. A design-thinking approach should employ mixed-methods data collection of those who administer vaccine programs in Sub-Saharan Africa so as to elicit, qualitatively, their perspectives on costs. Following the qualitative phase, a universal categorization of costs should be designed, and quantitative cost data should be collected using it. To determine how robust cost types are to the categorizations, multiple people at each participating study site should categorize the costs themselves so as to allow for the posterior comparison of costs which are commonly miscategorized.

Finally, and perhaps most impactfully, further research is needed to assess the generalizability of the important finding that a private firm investing in reducing malaria among workers can pay for itself. If validated in other sites (with their own unique combination of worker types, epidemiological and meteorological conditions, geographic density, etc.), the finding that malaria control can be profitable could have important implications for the role that the private sector plays in the march towards eradication.

10.6 Reflection

All the conditions are right; so why do we keep getting it wrong?

From a purely technical perspective, conditions are ripe in many locations for malaria elimination. Though not highly effective, one-dose vaccine yet exists, many other factors are favorable for malaria control: knowledge on the parasite is certainly sufficient: the scientific and public health communities know more, and share more, in regards to malaria than at any time in history. Preventive measures are advanced and effective: population-level interventions like larviciding, outdoor space spraying, and water management are feasible even in remote areas, and individual-level prevention measures, ranging from indoor residual spraying to intermittent preventive treatment and insecticide-treated nets, have never been so widespread. These factors, combined with rapid economic development in recent decades in the most malaria-stricken areas of the world, might suggest that even eradication is not unfeasible¹.

Given all the apparently facilitating factors for reducing the burden of malaria worldwide, the obvious question arises: why has eradication not occurred? And even more worryingly, why has elimination progress in recent years stalled, with virtually the same number of cases in 2018 (228 million) as in 2010 (251 million) (World Health Organization 2019)? If all the conditions are *right* for large leaps forward in malaria control, then what are we doing *wrong*?

The answers to these questions are not immediately clear. What is clear, however, is that a deeper examination of the prerequisite conditions, facilitating factors, barriers, and incentives for control, elimination, and eradication needs to take place, using novel methods to try to understand why what *should* work hasn't worked. But this examination must go beyond the limits of one discipline, or the normal confines of what is considered to be the "health sector".

The structure may appear somewhat disjointed. That's because it is. As is the case with many doctoral students, my original vision for this PhD did not coincide neatly with reality, nor with what I considered to be the most pressing research needs as I learned more about the field. Unlike most doctoral students, however, the *transdisciplinary* nature of my program granted me sufficient intellectual liberty to *pivot* as I incorporated new knowledge, and new collaborations, into my research. If I were to summarize this process, I would call it "unintentional emergent design".

Whereas most doctoral theses go from the general to the specific, the flow of work in mine was backwards: from the specific to the general. I started with concrete, tangible, quantifiable research questions about specific projects and interventions. But the answers from each study simply provoked more questions, each of them progressively further from those domains where I felt most comfortable. If malaria control activities were profitable, why weren't more firms doing them? If more firms did them, how could their efforts be coordinated towards elimination? If massive, coordinate elimination efforts don't succeed in eliminating malaria, what non-traditional methods might do the trick? Can malaria elimination eradicate poverty, or is the causal pathway backwards? Is eradication even possible? These

¹ "Eradication" is defined by the World Health Organization as the "permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate activities".

are some of the questions which were not present in my original research plan, but ultimately came to define the studies I undertook.

On a personal level too, my PhD journey has been one from the specific to the general. When I began in 2016, I had a more firm concept of my own identity and role in the world of public health. I saw myself as an epidemiologist and data scientist, with a passion for numbers, disease control, and statistical analysis. I had just finished 3 years working in disease control at the Florida Department of Health, and I was ready to apply what I had learned there to the economics of malaria. Put simply, I thought of myself as the “subject” and the PhD as the “object”; that is, I was going to do something *to* the research.

What I didn’t realize, going in, was that the research itself was going to do something to me. The transdisciplinary method, which at the outset I had considered a minor annoyance or formality, was more powerful than I anticipated. Its *iterative* approach to knowledge acquisition - asking, re-asking, incorporating new viewpoints, generating new questions based on intermediary learnings - contrasted sharply with my much more *protocolized* mindset towards research, partly a vestige of my previous research and work experience, and partly a vestige of my own personality. By being forced to wrestle with research questions that emerged *during* (rather than simply before) the research process was underway, I was also obligated to embrace research *methods* that I had not originally set out to explore, such as bias-reducing interview techniques and qualitative data analysis. Ultimately, the journey broke down my previous constructed identity of my role in the public health and research landscape. In learning that the methods I felt most comfortable with were insufficient to answer the questions I found to be most pressing, I also learned that I needed to delve into new methods, seek new partners, and ask new questions. I describe this personal journey as one from the *specific* to the *general* because it has helped me escape from the restrictive (and reductionist) mindset I had at the beginning of this process, and has pushed me towards areas of knowledge-acquisition with which I previously felt a much greater deal of discomfort.

Two kinds of knowledge emerge from the research process: (1) the *specific* discoveries generated from the study itself (which are transferable - via publications, code repositories, presentations, and posters - to others), and (2) the *general* knowledge gained from the *experience* of conducting the research. The latter requires more intentionality and reflection (one of the advantages of the transdisciplinary approach), is harder to demonstrate publicly, and is far more difficult to transfer to others. But its effects are real. At the crossroads of epidemiology and economics, public health and private firms, lofty goals and concrete data endpoints, is a world unto itself: the world of malaria. Navigating this world successfully (and by this I mean, eventually, getting to eradication) will require re-inventing the way we think about malaria; and this re-invention requires a crossing of disciplines, a leap out of the confines of the public and academic sectors, and a hefty dose of self-criticism and doubt. In other words, it requires a degree of re-inventing one’s self. For me, this PhD was a start at exactly that.

10.7 Concluding remarks

Malaria can be both prevented and cured. And technically speaking, it can be eliminated in areas, and therefore eradicated globally. Why, then, do these solvable problems go unsolved?

My ingoing hypothesis with this research was that there existed an *insufficiency* of incentives for individuals and firms to invest meaningfully in eradication-related measures. However, the findings of these studies challenged that hypothesis while also complicating it somewhat. The theory that incentives were insufficient for individuals to take malaria control measures was roundly shot down by the finding that nearly 100% of Gambians sleep under a mosquito net. And insufficiency of incentives also did not explain the vast landscape of corporate social responsibility geared at malaria control. Finally, in the qualitative analysis of the hundreds of comments from malaria researchers regarding the obstacles to eradication, nearly none pointed towards incentives, instead highlighting technical, political, and biological challenges.

Insufficiency of incentives certainly plays an important role in the case of some measures not being implemented, but it is clearly not the only role. On the contrary, if there is any lesson to be taken from the study of the sugarcane plantation, it is that some firms are willing to carry out malaria control activities despite an *ignorance* of the incentives (that is, not have quantified whether the program was cost-generating or revenue-generating). Complexity, not a lack of incentives, is the driving factor here.

The economics of malaria control clearly go beyond simple incentives. Accordingly, scaling up malaria control in endemic countries (a necessary prerequisite to eradication) will require more than just incentivization, but also:

- Alignment (i.e., foreign firms working in coordination with the government so that corporate social responsibility activities are not misdirected);
- Clear communication (i.e., researchers speaking openly about their pessimism regarding timelines espoused by the institutions which often fund them);
- Organization (i.e., data around disease control activities like vaccine campaigns being standardized, readily shared, and openly audited for quality assurance);
- Innovation (i.e., working across disciplines and sectors to experiment rapidly with new methods and measures).

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